THE CLINICAL PHYSIOLOGY OF THE LUNGS

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To

K. R. D.

In grateful recognition

of her assistance

in the preparation of this book

PREFACE

A series of lectures which I gave in 1944 on pulmonary edema and inflammation resulted in the publication of a small monograph (1).* They resulted, too, in systematizing and clarifying my ideas concerning a number of clinical conditions frequently met, but, because of the highly specialized structure and function of the lungs, hard to understand The lectures recounted research experience and correlated material which went back to 1921, when, at the request of Francis W Peabody, I devised and, with the help of Herrman L. Blumgart, carried out experiments to demonstrate the readiness with which stasis of blood in the lung capillaries excludes air from the alveoli.

During the ensuing years, aided by many students, I carried on in my laboratory a series of experiments directed at explaining and evaluating physiologically such frequent clinical experiences as obstruction of the pulmonary arteries and veins, the production and removal of transudates and exudates, the entrance of air into the lung capillaries, and other clinical problems All of the numerous experiments were performed on anesthetized animals. They necessitated the creation of new methods for exposing and cannulating the different pulmonary vessels, for separating and collecting air from the two lungs, and other technical procedures hithertofore accomplished only upon animals with open chests and under artificial respiration—very different physiological conditions from those existing in naturally breathing animals with closed chests.

These efforts seem labored and artificial compared with techniques available today, when catheterization of heart and blood vessels is readily accomplished in animals and in man, and without the necessity for anesthesia. Yet I believe the results we attained have been perfected, not superseded, by this later work.

It was my purpose in a second series of lectures, given during

*See References, Chapter I.

the spring of 1950 at The Medical College of the State of South Carolina, to extend what I had presented in 1945, utilizing for this purpose data obtained by many investigations during and since the war on animals and on man. These lectures, in their turn, I have assembled and amplified into the present monograph; and since much of the material presented is under active discussion and research, I have tried to write informally and suggestively, as is appropriate to an effort designed to give impetus to thinking.

In planning the lectures, I was guided by what I considered the basic structural components of the lungs for accomplishing the constant adaptations which occur during breathing. One begins, naturally, with the arteries; then considers the veins and capillaries, next the bronchioles; the nerves; and, finally, the lymphatics.

I have avoided discussion of gas exchange, except in so far as it applies directly to our problem. This may be an error; but an attempt at its consideration would extend unduly my primary objective of considering adaptive reactions in the lungs themselves, and not the effect of these reactions on the whole body.

It is my experience that, as a person grows older, he develops a wholesome reluctance to speak about subjects still very much under judgment and research, unless fortified by personal efforts in the field. For what follows you may be sure I can say with old Ulysses, as he reviewed the past, "I am a part of all that I have met."

Falmouth, Massachusetts CECIL K. DRINKER

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I

THE PULMONARY ARTERY AND ARTERIOLES

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The Pulmonary Artery and Arterioles

THE PULMONARY artery arises from the left side of the base of the right ventricle and passes up and back for about 5 cm , to divide into right and left branches The diameter of the main trunk averages 30 mm , slightly greater than that of the aorta The wall of the artery is comparatively thin, with elastic tissue the main structural component This is also true of the branches Smooth muscle is, of course, present and is proportionally greater in amount in the small vessels, but the dominance of elastic tissue throughout the system is most important. Macklin (2) has demonstrated that the bronchi lengthen with full inspiration, and, since the arteries accompany the bronchi closely, it is essential that they follow bronchial changes smoothly—a correlation which could not readily occur were the arteries the highly muscularized tubes we find in the systemic circulation The pulmonary artery and its branches are supplied by both vagus and sympathetic nerves, but, so far as definite effects resulting in contraction are concerned, these are apparently of little consequence, and are probably mainly afferent

In considering the regulation of blood flow through the lungs, confusion has arisen from facts which characterize the systemic circulation The systemic circulation is organized as a series of shunts, the objective being to provide oxygenated blood to tissues which are active Thus, if one passes from rest into physical activity —running, for example—a general constriction of vessels in the abdomen occurs, with a concomitant opening of arteries and capillaries in the muscles This adaptation is brought about in large degree by nervous regulation The lungs, on the other hand, are quite uniform in structure No one part is advantageous over another for providing oxygenation of the blood, and all parts, saving only the walls of the large vessels and bronchi, have an available supply of oxygen

from the alveolar air. Furthermore, the lung tissue is a slight user of oxygen, the diffusion of oxygen and carbon dioxide between air and blood being a process requiring no expenditure of energy. In physiology it is dangerous to use teleological reasoning, but I find it very hard to see what advantage would be offered by centrally controlled reactions of the pulmonary blood vessels which resulted in shunting the blood to one part of the lungs and closing off another. In my view, the integration of the blood flow through the lungs with the needs of the body is achieved by the structure of the lungs themselves, not by any complexity of central regulation.

This does not mean that the pulmonary arteries and arterioles are incapable of contraction nor that the amounts of blood are the same throughout the lung tissue The blood vessels possess sufficient smooth muscle to bring about constriction and to sustain it against the force of right ventricular contraction. In common allergic states, it is inescapable that the blood vessels are contracted with the bronchioles. In certain animals strong and persistent contractions result from intravenous injections of foreign protein. Thus, if one gives horse serum intravenously to a cat, there is an immediate and extensive rise in pulmonary arterial pressure; and the same sort of reaction accompanies anaphylactic shock in the rabbit and to a lesser degree, in the cat (3) Anoxia, too, causes vascular constriction—at once released on breathing pure oxygen (4). These reactions are apparently direct effects upon the smooth muscle—that is, they are inherent in the lungs themselves and are not dependent upon reflex nervous influences

In addition to the pulmonary artery and its branches, the lungs possess systemic vessels, the bronchial arteries and capillaries These supply the bronchi and provide vasa vasorum for the pulmonary arteries and veins Reactions in this system are probably similar to those in other parts of the body, but do not seem to be so intense.

In a normal man of 70 Kg (154 lbs.), with a total blood volume of about 6,000 cc., the pulmonary artery, capillaries, and veins contain 500 to 1,000 cc of blood This volume fluctuates, becoming greater on inspiration and being uniformly greater when the lungs operate at larger size, as in physical exercise, when the pulmonary blood volume may be one-fifth of the total blood volume, or in the normal man, 1,200 cc

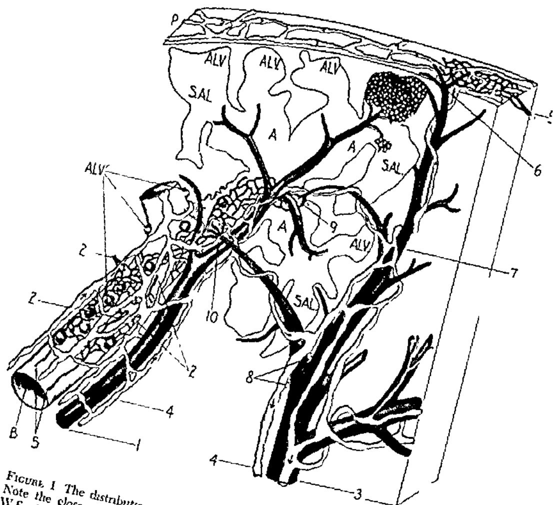


FIGURE 1 The distribution of arteries, veins, and lymphatics in a lung lobule Note the close association of the artery with the bronchus (From MILLER, W.S *The Lung*, 2nd ed, Fig 61, p 75 Springfield, Ill, Charles C Thomas, Publisher, 1947)

By virtue of their large capacity and their extreme elasticity, the lungs are an important potential reservoir of blood. Thus, if cardiac inflow is high and the left ventricle becomes unable to expel the large volume of incoming blood as fast as it is provided, blood may accumulate in the lungs, to be slowly emptied out as the heart becomes able to deal with it One of the handicaps to physical work experienced by patients with emphysema is due to diminution in number of the lung capillaries and loss of lung elasticity, so that the patient is deprived of the beneficent reservoir effect so definitely present in normal lungs.

The pulmonary capillaries offer a vast surface for gas diffusion, about 140 square meters Three to 5 liters of blood traverse these vessels each minute, and this amount readily reaches 20 liters during hard exercise It is estimated that each corpuscle passes through the pulmonary capillaries in one second, a figure which must vary markedly in different parts of the lungs at the same moment, but which probably becomes increasingly uniform as cardiac output rises.

Figure 1 is a diagram showing the arrangement of the vessels in a lung lobule The pulmonary arteries are closely associated with the bronchi, and branch to follow each bronchiole until a respiratory bronchiole is reached and capillary nets begin to appear The final ramification is over the alveolar surfaces, where the venous net begins The lung capillaries have scarcely any individual length They form a close-meshed net, the mesh of which is often less in diameter than the capillaries which form it (Figure 2) Through this net the red cells pass as a thin sheet over the alveolar surface A network very similar to that in the mammal is found in the lung of the frog, where it may be observed microscopically under very normal conditions

The blood corpuscles pass through the capillaries usually in single line and often undergo marked deformation as they twist around corners The elasticity and ductility of the blood cells is ordinarily not realized If the cells are stiffened even slightly, as by brief immersion in dilute formalin, they at once block the flow of blood and death ensues. The deformation and return of a corpuscle to normal shape are shown in Figure 3 from a motion picture film made by Krogh (5) In discussing the elasticity of the blood cells,

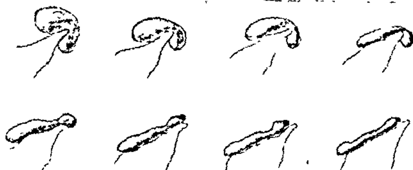


FIGURE 3. The deformation and return to normal shape of a red cell passing

Krogh points out that corpuscles frequently pass through filters which hold back far smaller particles, and that this ability to slip through small holes—smaller indeed than the diameter of the cells—is probably an important factor in the passage of red cells through the intact walls of capillaries. This passage of red cells through capillary walls invariably occurs when blood flow in a capillary stops or is much slowed. Little or no pressure is needed to bring it about, and there is no actual hemorrhage as evidenced by masses of cells outside the vessel wall. Corpuscles pass through without permitting leakage of plasma, much as a needle may be pushed through a film of gelatin without in the least affecting the integrity of the film.

The pressure in the pulmonary artery and its larger divisions is not high. Many figures for this are available both in animals and in man. Using catheters passed into the artery, Riley and his associates (6) obtained typical figures for three normal men between 26 and 36 years of age. Mean pulmonary pressures in these men while at rest averaged 13 mm. of Hg; [illegible] brachial [illegible] res, taken simultaneously, averaged [illegible] Similar [illegible] have been made by many other[illegible] Is must, [illegible] estab-

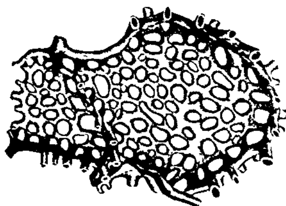


FIGURE 2 Reconstruction of a network of capillaries in the walls of an alveolus (From MILLER, W S. *The Lung*, 2nd ed, Fig. 62, p 76 Springfield, Ill, Charles C Thomas, Publisher, 1947)

lished, but what interests us far more are measurements of the degree to which the pressure may rise or fall in normal persons during familiar experiences and in subjects with diseases of the heart and lungs Contrasting with the values for rest, exercise in the three men cited above produced a slight lowering of pulmonary arterial pressure—a mean value of 10–11 mm of Hg as against 13 mm at rest This probably expresses the fact that the pulmonary vascular bed of the normal lung enlarges during increased breathing to a capacity overshadowing the cardiac output, and the lung vessels are thus not subjected to the strain experienced by the less expansile systemic group. If exercise is accompanied by anoxia, as may often be the case, a different result ensues Motley and his collaborators (7) found that acute anoxia, induced by breathing 10 per cent oxygen in nitrogen for short periods, caused a uniform increase in the mean pulmonary arterial pressure of five normal subjects of from 13.1 mm to 23 mm Hg, with a rapid fall to normal when the anoxia was relieved Pulmonary hypertension occurring as a partial result of anoxia—for example, in extreme exercise—is a frequent experience of man.

Experiments upon anesthetized animals with chests closed and breathing naturally confirm the above finding (8), and have added the fact that inhalation of pure oxygen causes pulmonary arterial pressure to fall, a matter of some importance when considering the effects of oxygen inhalation in cardiac failure and in asthma

Pulse pressure in the pulmonary arteries is usually higher than the mean pressure, an expression of the very low resistance offered by the lung vessels All of these reactions are direct effects upon the smooth muscle in the pulmonary vessels They are thus inherent in the lungs themselves So too, the regulation of blood flow through the lungs—a flow which changes smoothly with the needs of the individual—is inherent in the general structure of the lungs and in the amount of blood supplied by the right ventricle It does not depend on nervous effects exerted within the lungs themselves

There is a point which should be made here In spite of the great elasticity of the lung vessels, including the capillaries, it is true that when the left ventricle fails to deliver all the blood coming to it—and this is something which occurs briefly in normal persons subjected to excessive physical effort—pressure in the pulmonary artery

rises. The effect is seen in exaggerated degree when cardiac lesions are present or in pulmonary disease, such as chronic emphysema, in which the ultimate distribution of the pulmonary vessels is decreased and the lung elasticity lessened. Riley and his associates (6), for example, report a patient with chronic emphysema whose normal pulmonary artery pressure at rest of 13 mm. of Hg rose to 19 mm on his sitting up, and to 43 mm. during work.

Finally, alveolar air pressure can cause compression of the lung capillaries and impose varying degrees of resistance In the dog, an increase of air pressure in the trachea to 80 mm of Hg completely blocks pulmonary blood flow, and death is prompt.

Interest in breathing oxygen at pressures above atmospheric, in order to secure the highest possible oxygenation of the blood, and in the use of artificial respiration apparatus which pumps oxygen to the lungs with a blast of positive pressure, brings to notice this matter of tolerable alveolar air pressure. It is safe, apparently, even in infants to use positive pressure lung inflation up to 14 mm. of Hg Possibly a higher limit might be set, but the issue is one which demands conservatism Let me illustrate In training for submarine service in the past, candidates were required to escape from a tank simulating a sunken submarine. The trainee wore a device for oxygen breathing with a mouthpiece and nose clip He inhaled the oxygen naturally and exhaled through a valve in the appliance. In order to qualify for the United States submarine service, trainees were required to escape from depths to about 50 feet. The young men undergoing such tests were in the best of health, yet during our early escape training five deaths occurred. The cause of these accidents was soon discovered When any normal person puts his face under water he holds his breath tenaciously—a compelling reflex If, with breath held, a trainee rose 50 feet to the surface, the air in his chest expanded as the pressure was reduced. This took place rapidly, and not only was blood flow through the lungs reduced but air was forced from the alveoli into the lung capillaries, bringing about fatal coronary and cerebral embolism. The remedy was obvious Trainees must wear the mask near the surface and learn above all else to exhale. I have watched experienced men come up 50 feet exhaling steadily and never taking a single breath from the apparatus. Their breathing was accomplished by the increasing

volume of oxygen in the lungs, which enabled them to dispense with inspiration.

It is thus possible for air in the alveoli to impede pulmonary blood flow and to cause increase in pulmonary arterial pressure. Reciprocally, it is easy to show that overstuffing of pulmonary capillaries, as is seen in cardiac disease, may so splint the alveolar walls and encroach upon alveolar air space as to limit the amount of air which is able to reach the alveoli.

Infarction

One of the best ways to learn something of how the pulmonary circulation is regulated is by study of the events following obstruction of the arteries. The problems of diagnosis and management of pulmonary embolism are much in the foreground today. Methods for treating these cases, whether by administration of anticoagulants or by ligation of veins, appear steadily. But the physiological effects of arterial block in the lungs, and even more the causes of blood clotting in remote and apparently uninjured veins, are poorly or not at all understood. We used to, and still do, fear pulmonary embolism after surgical operations, particularly in the pelvic region. But in recent years we have learned that lung embolism often occurs in individuals apparently in the best of health, causing symptoms which formerly we vaguely called ideopathic pleurisy or pleurodynia.

Given a healthy heart, such as is found in a young adult, it is surprising to realize what large degrees of sudden pulmonary arterial obstruction may be withstood. In 1923 Haggart and Walker (9), in experiments on anesthetized cats with closed chests and breathing naturally, were able to place a clamp, such as is shown in Figure 4, on the pulmonary artery or one of its main divisions. In such a preparation the vessel may be closed by means of the screw, and by reading the scale upon the instrument, one may ascertain the degree to which the vessel is occluded. In Haggart and Walker's experiments if the left branch of the pulmonary artery was clamped, the pulmonary artery pressure—measured by means of a cannula which did not interfere with blood flow—rose for a short time about 29 per cent. This did not cause any significant change in systemic blood pressure nor in cardiac output, and resulted in but moderate

increase in breathing. In similar experiments by Gibbon and his co-workers (10), until almost 60 per cent occlusion of the pulmonary artery was effected, general circulatory failure did not occur. These findings express quantitative results. Other investigations have

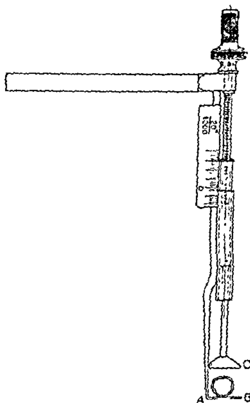


FIGURE 4 Clamp for applying measurable degrees of occlusion to large pulmonary vessels (From HAGGART, G.E., and WALKER, A.M *Arch Surg*, 1923, 6, 768, Fig 3.)

shown that healthy animals withstand even higher degrees of vascular block—up to 70 and 80 per cent.

Shortly after pulmonary infarction, pleurisy is frequent—indeed, may be the single complaint of the patient. This is due to the fact that blood soon escapes into some of the alveoli involved; and if the infarction is near the lung surface this blood often reaches the

visceral pleura, where clotting occurs, bringing about adhesion of pleural surfaces and consequent pain At the same time rales may be heard over the painful area and, as time passes, bloody sputum often appears Such findings indicate the filling of alveoli with exudate and a progressive degree of airlessness in the region. X-ray examination may show an ill-defined shadowy area—less clear-cut evidence than one might expect—and frequently the x-ray is of no help at all, diagnosis depending upon history, pleuritic pain, rales, and eventually upon cough with bloody sputum Seen at autopsy, lung infarcts are commonly marginated livery lesions, containing little or no air On section, they are filled with dark blood Such solid infarcts, hemorrhagic in character, occur most readily in lungs already somewhat congested or filled with slowly flowing blood.

When a medium-sized branch of the pulmonary artery is plugged by an embolus, blood flow through the region supplied may be greatly slowed or practically absent At the same time, there is no interference with air movement into and out of the alveoli, so that at first the tissue is fully oxygenated The statement is made that, with blockage of blood flow, there is a reflex contraction of bronchioles to the area, but I find no real evidence for this, indeed, there is substantial evidence to the contrary Churchill and Agassiz (11) were able to tie cannulae in the right and left bronchi of the cat (Figure 5) and to place clamps around the corresponding pulmonary arteries and veins, which could thus be occluded and released at will In this preparation, the air from each lung could be collected separately The chest was closed and the animal breathed naturally "No change of significance was found in the relative volume of air moved by the two lungs after occlusion of one branch of the pulmonary artery" This can only mean that, though the blood supply to one lung was cut off completely and abruptly, there was no immediate effect upon air movement, such as would have been the case had some reflex from the occluded artery altered the caliber of the corresponding bronchus Even when occlusion lasted fifteen minutes there was no bronchial effect, and, on release of the clamp, relations of air moved by the two lungs returned to the levels existing before occlusion This is well shown in Figure 6

The sequence of events in the lung following blockage of a fair-sized branch of the pulmonary artery is still poorly understood

Though there can be no doubt that the part of the lung supplied by the occluded vessel tends to become solid and airless, the rate at which this happens varies markedly in different patients. The tendency is toward the establishment of a typical, solid infarct, such as the pathologist delights to demonstrate at the autopsy table, but often the expected result is incompletely realized.

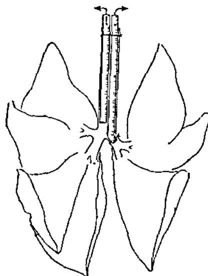


FIGURE 5 Diagram of method for separating the air breathed by the two lungs (From CHURCHILL, E D, and AGASSIZ, A *Am J Physiol*, 1926, 76, 8, Fig 1)

I believe some degree of reflection upon the situation will help to explain what happens. The flow of blood through the lung capillaries depends upon the contraction of the [illegible] ventricle and upon the movements of breathing If arter[illegible] suddenly sl[illegible] the flow of blood, in spite of mode[illegible] [illegible]ed bre[illegible] slowed and corpuscles begin to pile [illegible] capillari[illegible] though connect[illegible] [illegible] vessels wh[illegible] been [illegible] lead blood into [illegible] [illegible]l area, t[illegible] [illegible] to [illegible] masses of visco[illegible] [illegible]y be q[illegible] so an[illegible] blood piles up, [illegible]blishing [illegible]t Th[illegible]

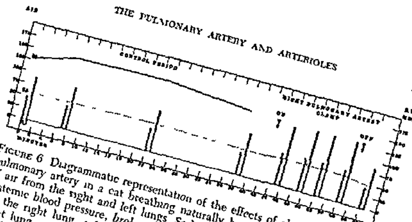


FIGURE 6 Diagrammatic representation of the effects of clamping the right pulmonary artery in a cat breathing naturally but with separate collection of air from the right and left lungs Sodium barbital anesthesia *Solid line*, systemic blood pressure, *broken line*, percentage of total ventilation moved by the right lung, *solid columns*, cubic centimeters of air moved by the right lung per minute, *open columns*, cubic centimeters of air moved by the left lung per minute, *shaded columns*, total ventilation in cubic centimeters of air per minute Reading from left to right, the two arrows indicate the points of occlusion and release of the right pulmonary artery *Ordinates*, millimeters of mercury, percentage, and, multiplied by 10, cubic centimeters of air *Abscissae*, time in minutes (From CHURCHILL, E D, and AGASSIZ A *Am J Physiol*, 1926, *76*, 10, Fig 2)

is slow, resulting in filling of alveoli with bloody exudate, escape of blood onto adjacent pleural surfaces, and some degree of pleurisy Obviously, too, the establishment of infarct solidity is related to the condition of the patient when embolism takes place. If some degree of passive congestion and pulmonary stasis is present, blockage of blood flow through the affected region will be more rapid and complete So too, if pleuritic pain splints the affected lung, respiratory assistance to the movement of blood will be lessened locally or practically absent In experimental animals in fine circulatory condition, it is surprising to occlude the right branch of the pulmonary artery for fifteen minutes, as in the experiment shown in Figure 6, and on release of the occlusion, to see everything become normal almost at once This means that a healthy right ventricular muscle has maintained some degree of corpuscular progress through the infarcted area by means of connecting vessels, and has thus limited the degree of capillary stasis and blockage of blood flow

In matters of this sort, when one is tempted to transfer observations upon animals to man, it must be remembered that so far as the circulation is concerned our laboratory animals represent man

at his very best. In many years of experiment, I have encountered but one instance of mitral stenosis in a dog. Occasionally one comes upon a cat with surprisingly high blood pressure. But ordinarily animals with circulatory disorders do not live long. Man, on the other hand, is increasingly successful in prolonging the life of handicapped individuals; and so provides an enlarging reservoir of subjects, who, if victims of pulmonary embolism, will tend more and more to establish solid, airless infarcts, highly gratifying to the x-ray man in their sharp outline and often, unfortunately, to the pathologist who demonstrates them at autopsy.

There is a further agency which affects the type of infarct. It is the bronchial circulation. The bronchial arteries are systemic vessels. They receive vagal and sympathetic nerves; the former when stimulated, causing dilatation, the latter constriction. Their reactions to a number of drugs and to abnormal concentrations of oxygen and carbon dioxide resemble those of other systemic arteries (12). The blood pressure in these vessels is much higher than in the pulmonary arteries. Most of their blood enters the pulmonary veins, but under normal conditions the bronchial arteries reach capillary size before beginning to join the pulmonary circulation. This means that the systemic blood pressure, to which they are subject, is ineffective in causing abnormal pulmonary capillary pressures, being dissipated promptly in the vast area of the pulmonary capillary net. It is, however, inescapable that in regions where a pulmonary artery has been blocked blood from bronchial arteries will still flow into the capillary net, and can thus influence the forward movement of blood and perhaps assist in the prevention of stasis. Measurements in the dog of the volume of bronchial artery blood entering the pulmonary circulation per minute have shown it to be but a fraction of the total. Possibly in patients with hypertension additional blood may enter by this route. If this addition were large enough, stagnant blood in a region of pulmonary arterial block might be kept in movement towards the left side of the heart and solid infarction in some degree prevented. It is equally probable that the increased inflow from the bronchial artery supply would simply add blood to the infarcted region, and so induce more rapid solidity.

Hypertension, so common in man after the fortieth year, is thus



FIGURE 7 Enlargement of a branch of the bronchial artery in a human lung removed from a patient with bronchiectasis Two large vessels cross the lower part of the illustration The upper and darker is a bronchial artery, the lower, a corresponding pulmonary artery The bulbous object on the left side of the photograph is a bronchiectatic sac, and at its top the bronchial and pulmonary arteries anastomose (From LIEBOW, A A, HALES M R, and LINDSKOG, G E *Am J Path*, 1949, 25, 227, Plate 29 Fig 5)

a factor bearing upon the physical characteristics of these lesions. There is another group of facts relative to the bronchial vessels which is important These vessels in normal men are small in size and vary in number Their variability of caliber is ordinarily not great, but recently Liebow, Hales, and Lindskog (13) by injecting surgical specimens of human lungs have shown that in regions about bronchiectatic cavities the bronchial vessels are enlarged, and that there is anastomosis with the pulmonary arteries in terms of vessels often 1 mm or more in diameter Figure 7 is a photograph of part of a human lung in which the pulmonary and bronchial arteries have been injected. The tissue was removed at surgical operation on account of bronchiectasis Two large vessels cross the lower part of the illustration The upper of these is from a branch of the bronchial artery, and the lower, about of equal size, is from the pulmonary artery Both vessels branch and ramify over a large bronchiectatic sac which occupies the upper left quadrant of the illustration Anastomosis between these branches is seen at the top of the illustration In fifteen of eighteen specimens of lung from patients with bronchiectasis there was great enlargement of the bronchial arteries and numerous anastomoses of these vessels with the pulmonary arteries

An even more significant observation of the ability of the bronchial circulation to replace the pulmonary flow is the evidence presented by Gray and his associates (14) that in chronic pulmonary disease with anoxia collateral channels between bronchial and pulmonary arteries partially overcame the anoxemia from venous blood shunted through a poorly oxygenated lung into pulmonary veins This collateral flow was very large and had a decided effect on the oxygenation of the arterial blood

The normal function of the bronchial arteries is to provide vasa vasorum for the pulmonary arteries and veins and for the bronchi The bronchial vessel effluent in the main enters the pulmonary circulation Bruner and Schmidt (12) showed that the normal bronchial artery blood flow in the dog was about 27 cc per minute This is but a small fraction of the cardiac output In contrast, Bloomer and his associates (15) found that in dogs which survived ligation of one pulmonary artery for 18 to 20 months there was a flow of blood through the bronchial arteries in excess of 900 cc. per minute

This is so large a flow as to make it possible that in advanced bronchiectasis pulmonary hypertension may occur. But in this regard Liebow and his co-workers (13) cite Cournand's (16) evidence that in man even the removal of an entire lung, with the necessity that the whole cardiac output pass through the remaining lung, does not result in hypertension, the capillary bed being so vast and so easily distended as to accommodate all the blood normally traversing both lungs without a rise in pressure. See also (17).

There is a final point relative to the bronchial vessels which is of importance, and that is their ability to react locally to irritation. The bronchial vessels are *distributed widely to the pulmonary vessels* and bronchioles. Certainly the latter are highly susceptible to inflammation, the bronchial mucous membrane readily displaying "reactive hyperemia." Whether this reaction, so fundamental in the skin and mucous membranes, occurs within the lung itself—that is, *through the pulmonary vessels*—I do not know. The fact that the lungs lack sensory nerves, except in so far as they are plentiful in the mucosa of the bronchi, makes it very probable that irritative stimuli within the lung parenchyma fail to produce the typical series of events which lead to inflammation. This is a matter to which I will return later in the chapter upon the nerves of the lungs.

Inherent Regulation of Blood Flow

Finally, we come to the regulation of blood flow through the lungs There is sufficient smooth muscle in the pulmonary arteries and arterioles to bring about strong and sustained contraction, and probably the endothelium of the pulmonary capillaries possesses a tonic tendency to reduce in size, just as is the case for systemic capillaries

Neither of these instances of contraction is of great consequence in the normal constant adjustments of flow which take place in the lungs. If we use the simple illustration of physical exercise, it will *perhaps clarify my* views. On passing from rest into work, the heart beats more rapidly and forcibly. The systemic blood pressure rises. Inflow of blood to the heart is greatly augmented. These changes are due, first, to re ulation throu . The faster, more vigorous heart beat is sion of sy stimulation; the increased blood pre expres traction of



FIGURE 8 The elastic fibers surrounding an alveolar sac Semi-diagrammatic (From MILLER, W S *The Lung*, 2nd ed, Fig 41 p 54 Springfield Ill, Charles C Thomas Publisher, 1947)

abdominal vessels and the larger cardiac output. While local changes due to acid metabolites, and possibly to histamine-like compounds, take part in the totality of the systemic circulatory adjustment, it is pre-eminently something regulated through the central nervous system Coincident with these circulatory changes, there is a marked increase in rate and depth of breathing These changes, too, are mediated through the respiratory center and allied centers, where stimuli arise as a result of chemical alterations in the blood and where the smoothness of respiratory adjustment is enhanced by afferent stimuli from nerves in the lungs themselves

In my opinion, no similar regulation of the pulmonary circulation exists, except in such rudimentary degree as to be merely a curiosity of painstaking experiment It is an obvious fact that as breathing increases in volume, as a result of exercise or of inhaling carbon dioxide or from oxygen lack, the size of the lungs changes, there being a prompt adaptive increase in size accompanying need and a return to normal size when the need is past It is not difficult today to measure pressure in the large pulmonary vessels, and to learn something of the amount of blood in the lungs and of the rate at which the blood goes through them. All of these variables might be affected by vasomotor adjustments, but a number of more subtle inherent arrangements govern the pulmonary circulation and anything so straightforward as vasomotor regulation is far from the mark.

Let me summarize the factors in the lungs themselves which passively adapt these organs to alterations in blood flow necessitated by systemic needs.

1. The pulmonary vessels are highly elastic and elastic tissue is widespread throughout the lung parenchyma Figure 8 shows the elastic fibers surrounding an alveolar air sac and Figure 9, the distribution of elastic fibers and smooth muscle on a bronchus.

The air in the lungs, with unobstructed tracheal outlet, provides a cushion, changeable in volume and at the same time altering little in pressure The systemic vessels possess no such flexible environment. There is a definite tissue pressure outside of them.

2 The pulmonary arterioles are short and the capillary bed is an immense mesh in which no single vessel has real length. This mesh increases in extent and capacity with inspiration, but the alveolar

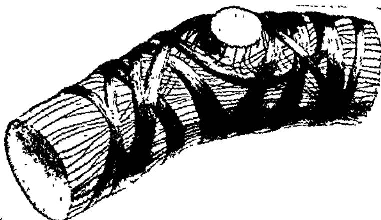


FIGURE 9 Elastic fibers (*fine lines*) and bands of smooth muscle about a large bronchus Semidiagrammatic. (*From* MILLER, W.S : *The Lung*, 2nd ed , Fig 40, p 53. Springfield, Ill., Charles C Thomas, Publisher, 1947.)

capillaries forming the net over the alveolar surface, and so in relation to the alveolar air, present the same opportunities for aeration of the blood passing through them, whether the alveoli are widely and universally open or whether, as during rest, some of them receive but little air and few capillaries conduct blood.

You noted, perhaps with surprise, that the pulmonary arterial pressure in three healthy young men fell slightly during exercise But this is not surprising when you consider that as the respiratory movement became larger the vascular bed also enlarged, and that, even though the output of the right ventricle increased, the blood passed through the wider circuit so readily that an increase of pressure was unnecessary. Indeed, and advantageously, the reverse occurred.

3. In spite of elasticity and adaptive capacity of the lung vessels, failure of delivery of blood by the left ventricle means backing up *in the lung vessels*, and under these circumstances, given a reasonable competent right ventricle, pressur e pulmona ery will increase This increase will gradu to the s and will promote pulmonary edema

4. The regulation of lun quir ng bo is accomplished by the e

bronchi and by the smooth muscle of these structures, together with bands in the lung parenchyma and under the pleural membrane.

I doubt if any fact brings home the inherent ability of the lungs to meet all that comes to them more vividly than the readiness with which man continues to live quite competently after the removal of an entire lung. It is true that such mutilated individuals must live relatively quietly, since they have lost so much of the vast margin of safety which the huge lung surface provides them But they are not helpless invalids, and even their greatly reduced lung volume accommodates the increased blood flow of mild physical work

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II

THE PULMONARY VEINS AND CAPILLARIES

PULMONARY EDEMA

THE BLOOD delivered to each lobe of the lungs is collected into veins, which, in turn, unite into the right and left pulmonary veins and enter the left auricle These veins lack valves and the unidirectional movement of the blood they contain is due to right ventricular contraction The fact that overfilling of the superior and inferior cavae and the right auricle causes a faster heart beat—the Bainbridge reflex—has led investigators to look for reflex effects due to stretching of the pulmonary veins These have not been found The walls of the pulmonary veins possess a well-developed media with circular fibers of smooth muscle, not unlike an artery.

Abrupt blockage of the pulmonary veins, similar to arterial embolism, seldom occurs In endocarditis mural thrombi on the wall of the left auricle may extend gradually into the pulmonary veins, and thus become a final factor in desperate illness

Churchill and Agassiz (1), working with cats under sodium barbital anesthesia and with chests closed, found that complete occlusion of the left pulmonary veins was not immediately fatal to the animal In such an experiment the vessels of the left lung were filled with imprisoned blood, yet in the supine, quiescent animal systemic blood pressure fell but slightly, expressing the fact that even the large amount of blood isolated in the lung was countered by systemic vasoconstriction, so that reduction in coronary blood flow and blood supply to the medullary centers did not cause immediate death

Occlusion of the right pulmonary veins is more serious and proved, in Churchill and Agassiz's experiments, fatal at once if the vein clamp was tightened rapidly At best, systemic blood pressure fell abruptly and but short periods of complete occlusion were tolerated In Figure 10 the effects are shown of left and right vein occlusion on systemic blood pressure The left veins were blocked first and after a time released The more serious effects of right vein occlusion are evident in this figure

Since ligation of pulmonary veins draining parts of the lungs had been tried as a means for treating tuberculosis, Swan and Mulligan (2) ligated the veins from the right upper lobe in healthy dogs The primary reaction was severe vascular engorgement and hemorrhage into the lung In about four months the hemorrhage was

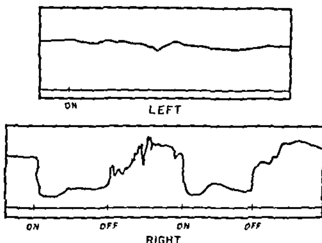


FIGURE 10 Tracings of systemic blood pressure showing effects of the occlusion of the right pulmonary veins (lower curve) as contrasted with the usual effects observed when the veins from the left lung (upper curve) are occluded by a clamp Redrawn from systemic blood pressure tracings (From CHURCHILL, E.D., and AGASSIZ, A.: *Am. J Physiol*, 1926, 76, 17, Fig 8)

absorbed, collateral venous channels were established through adhesions, and the lobe was apparently on the way to complete functional competence Ligation of the veins to the right lung was fatal. These findings are of interest in showing the ability of a lung lobe to become functionally normal even after severe mutilation

Mean pressure in the pulmonary veins during inspiration is 0 or subatmospheric At full expiration, pressure becomes positive but is low.

Histologically the lung capillaries are not distinctive, except in so far as they are grouped into an extraordinarily extensive and fine-meshed net. The net is coarser just under the pleura and adjacent

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ncy to net
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cells have very definite length before uniting with their fellows or entering a small vein Capillaries, such as those in muscle, serve tissue which varies markedly in metabolic rate between conditions of rest and work. It is in such tissues that dilatation and contraction of capillaries is prominent; and, as one would expect, these changes are most marked at points where capillaries originate from arterioles. Given a loose long-meshed net, change in caliber of capillaries at their points of origin from arterioles will be maximally efficient in affecting blood flow through the tissue In the lungs, on the other hand, close-meshed net formation with extensive communication between nets from lobule to lobule, while providing equal opportunities for distribution of blood over alveolar surfaces, does not lend itself to regulation of blood flow by capillary contraction and relaxation Microscopic observations of mammalian lungs have shown capillaries at one time conducting blood and at another time without blood flow (3). These findings have been interpreted as meaning independent contractile ability, but require further confirmation before any such regulatory function is granted Other direct observations (4) deny any regulatory function of blood flow to the capillaries, though admitting irregular changes in blood flow during observation

Pulmonary Edema

In spite of displaying nothing distinctive histologically, evidence slowly accumulates that the endothelium of the lung capillaries possesses very distinctive physiological properties When alpha-naphthyl thiourea (ANTU) is given to a variety of mammals and to frogs, it causes pulmonary edema (5). This result has been shown to be due to an increase in permeability of the lung capillaries, which—without showing any breaks in their walls—leak plasma into the lung parenchyma and into the alveoli, so as to fill the lungs completely and cause death. No other capillaries in the body are affected. This means some unique property of the lung vessels An equally distinctive and mysterious effect, again con-

fined entirely to the lung capillaries, has been described recently by Cameron and De (6) While studying experimental hydrocephalus, these two investigators made the surprising observation that when a freshly prepared fibrin mixture was injected through the foramen magnum into the cistern in rats and rabbits, acute pulmonary edema followed in five to ten minutes. Again, as with ANTU, the lung capillaries alone are involved, there being no edema in other parts of the body. This evidence, together with other facts and assumptions relative to the action of nerves upon the permeability of the pulmonary blood vessels, will be discussed in detail in Chapter IV.

The very close relationship of the lung capillaries to the alveolar air needs no comment The pulmonary arteries accompanying the bronchi reach arteriolar size and divide into scattered intercommunicating nets as the respiratory bronchiole is reached. At this point are found the first alveoli, and here gas exchange begins It has been thought that as the bronchial mucous membrane reaches the respiratory bronchiole it becomes a single layer of plate-like [illegible]

photomicrographs have been shown—practically invariably taken from diseased lungs—which display more or less complete rings, consisting of a single layer of cells which have been pushed out into the alveoli by transudate or exudate from the capillaries. The situation is particularly well ordered to separate capillary surfaces from alveolar air, and so to interfere with gas exchange. In my opinion, however, the bulk of most recent work (7, 8) is not in accord with the existence of a lining alveolar membrane. The alveolar partitions undoubtedly contain cells in addition to those of the capillaries, but they are not disposed in an orderly syncitium From the practical point of view, the facts are that when—through infection or from any other cause—excessive fluid and solutes escape the capillaries, the partitions containing them become swollen, and almost at once the abnormal fluid enters the alveoli and opposes a thickened barrier to transfer of gases between air and blood. If transudation continues, alveoli first and then bronchioles become blocked, and the process may go on until death from asphyxia occurs.

To function normally the lungs must be relatively dry. There is little room in them for anything except circulating blood and air. The flow of lymph from the lungs is slight unless undue capillary permeability exists. This state of affairs follows inevitably from the conditions which determine exchange of water between lung capillaries and the tissue in which they reside No one has succeeded in making direct measurements of pressure in these vessels, but a

both up and down—with variations in the vigor of right ventricular contraction, in the breathing, and finally in the position and general condition of the patient But under normal circumstances none of these influences causes high enough pressure to induce excessive filtration and edema. This is because the colloid osmotic pressure of the blood proteins, which holds water in the capillaries, is that of the normal blood and has a value between 20 and 30 mm. of Hg The escape of water into the alveolar septa is thus always slight, and will not become great enough to cause lung edema unless an abnormal rise in capillary pressure takes place, unless something increases the permeability of the capillaries, or unless there is serious depletion of plasma proteins so that the colloid osmotic pressure becomes too low to restrain the outward loss of abnormal amounts of fluid

When the pathogenesis of pulmonary edema was investigated years ago by Welch (9), we were left with the conception that pulmonary edema was caused by a disproportion between the contractions of the right and the left ventricle It was argued that if the left side of the heart became unable to expel all the blood delivered to it through the lungs by a healthy right ventricle, pulmonary edema developed This is true, but is not a generalization to be applied widely Welch used a few animals only—dogs and rabbits—and employed artificial respiration with the chest open Left ventricular failure was caused by compressing the aorta, by crushing the muscle of the left ventricle, or by both procedures The experiments were limited in number, were carried out under grossly abnormal conditions, and have never deserved the attention paid them The measures used may produce a brief period of stasis in the pulmonary capillaries, together with some increase in pulmonary arterial pressure But a brief

period of congestion gives no more than very slight transudation from the lung capillaries, particularly if the lungs are ventilated by artificial respiration so that anoxia does not occur.

Many experiments have been devoted to showing that obstruction of the pulmonary veins with piling up of blood in the lungs causes lung edema. As a rule, these experiments have been done with the chest open, so that the veins may be manipulated, and under artificial respiration, much in the manner of Welch's experiments, except that congestion was produced by less devastating procedures than gross obstruction of the thoracic aorta and mutilation of the left ventricle.

I believe it would require a good deal of time to cause severe pulmonary edema by increased capillary pressure alone In dogs, if one cannulates the right lymphatic duct, it is possible to collect all the lymph produced in the lungs except a small amount from the left upper lobe which enters the thoracic duct When the lung lymph is flowing from the right duct cannula—very slowly, as is normal for it—compression of the pulmonary veins will at once cause the flow to increase But the increase, though very evident, is not of significant volume Heightened [illegible]

restricted entrance into the blood offered by the right lymphatic duct causes lymph stasis, obvious pulmonary edema of conventional character is not seen. Something more than increased capillary pressure is necessary to cause edema

Many factors may be involved Of these anoxia is prominent. Lack of oxygen undoubtedly causes capillaries to become somewhat leaky all over the body, but anoxia alone is never a cause of other than slight edema I have often seen patients who have inhaled low concentrations of carbon monoxide for many hours so that their blood has not been more than half saturated with oxygen during the entire period If such patients survive, they may display cerebral or basal gangliar degeneration but they do not develop generalized edema during the period of anoxia.

The effects of anoxia alone in causing transudation from the lung capillaries are shown in Figure 11. In this case the animal breathed pure oxygen during about an hour. The flow of lung lymph increased

slightly during that time. The ventilation was then shifted to 8 6 per cent oxygen in nitrogen. The volume and rate of artificial respiration was unchanged. An increase in lymph flow occurred, which stopped abruptly when, at the end of an hour, ventilation with 100 per cent oxygen was resumed and the lack of oxygen in the alveolar air dis-

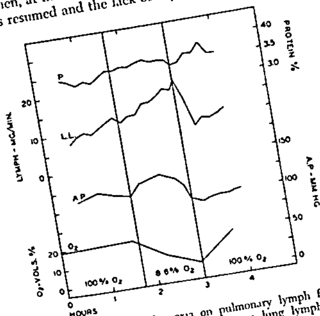


FIGURE 11 Effects of anoxia on pulmonary lymph flow and composition *Top curve*, protein in lung lymph in per cent *Second curve*, lymph flow from the lungs in milligrams per minute *Third curve*, systemic blood pressure in milligrams of mercury *Lowest curve*, oxygen content of arterial blood in volumes per cent Between the vertical lines artificial respiration was shifted from 100 per cent oxygen to a mixture of 8 6 per cent oxygen and 91 4 per cent nitrogen (From WARREN, M F and DRINKER, C K *Am J Physiol* 1942, 136, 212, Fig 4)

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Certainly pulmonary edema in varying degrees is seen most frequently in heart disease where compensation is failing In such

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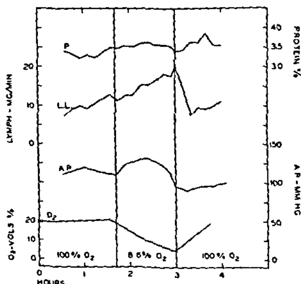


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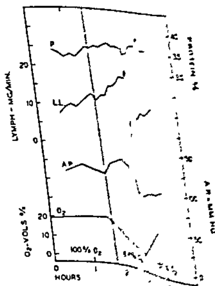


FIGURE 11. Effects of [illegible] and composition. To[illegible] per cent. Second [illegible] milligrams per [illegible] sure in milligrams of [illegible] tent of arterial blood [illegible] vertical lines artificial [illegible] cent oxygen to a [illegible] per cent nitrogen [illegible] 100 per C K Am J Ph[illegible] and 91.4 [illegible] Drinker. [illegible]

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Certainly pulmonary ede[illegible] quently in heart disease [illegible] is

patients edema is usually of slow development. When mitral stenosis is present, we ordinarily think that pulmonary arterial pressure is heightened and assume that capillary pressure is also raised. Neither of these assumptions need be true, except to a minor degree, provided the muscle of the ventricles is competent and the patient does not indulge in an undue amount of physical work. But if too much is required of the crippled heart increased transudation from the lung capillaries will begin and very soon many alveoli will contain transudate. Even though breathing is increased, normal oxygenation of the alveoli is not attained Indeed the hyperpnea is an expression of the failure in pulmonary gas exchange.

It seems to me inevitable that, as ordinarily encountered, anoxia and increased capillary pressure occur together. Just as soon as proteinized transudate enters alveoli some degree of capillary anoxia is experienced. The oxygen lack in turn increases capillary permeability and edema progresses.

Some years ago it was suggested, and shown through rather radical measures, that undue negative pressure in the alveoli could give the pressure in the lung capillaries a value high enough to cause abnormal transudation That is, if the capillary pressure was about of normal value, 10 mm of Hg, and inspiration was accomplished

caused dogs to breathe oxygen against inspiratory resistance for several hours, but edema did not begin until breathing was shifted to a mixture of 10 per cent oxygen, 85 per cent nitrogen, and 5 per cent carbon dioxide, this last being added to cause breathing to be increased several times Under these circumstances the condition of the animal remained excellent for 30 minutes, but abnormal transudation began at once and would have become pronounced. Here again two factors, alveolar anoxia and heightened negative pressure, have caused excessive capillary leakage. These facts are shown in Figure 12

It is true that there are poisons which cause acute edema of the lungs without immediate adjuvant factors. ANTU is such a poison. Soon after its administration pulmonary edema begins to develop, due at first to a direct effect on the lung capillaries, to an increase

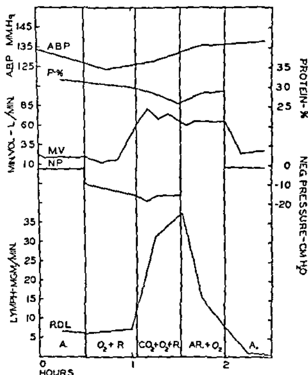


FIGURE 12 The effects of increased negative pressure in the alveoli upon the flow of lung lymph From the start of the experiment until the end of the first hour resistance to inspiration has resulted in negative intratracheal pressure, at the end of inspiration, of −10 cm of water Even

dioxide As a result the negative pressure at the end of inspiration became almost −20 cm. of water. R D L, flow of lymph from the lungs in milligrams per minute, N P, negative intratracheal pressure at full inspiration in centimeters of water, M V, minute volume in liters, P, per cent protein in lung lymph, A B P, arterial blood pressure in millimeters of mercury At the end of 1½ hours artificial respiration with oxygen was started and increased lymph flow subsided at once (From DRINKER, C K *Pulmonary Edema and Inflammation*, Fig 10, p 34 Cambridge, Mass, Harvard University Press, 1945)

in permeability to blood plasma, which continues inexorably to the death of the animal. Other poisons behave somewhat similarly but without the absolute specificity for the lung capillaries. In a Starling dog heart-lung preparation, where several hundred cubic centimeters of incoagulable blood circulate through the heart and lungs and through no other part of the body, after a period in which the lungs are apparently normal, pulmonary edema sets in The cause of this development is not known. It expresses either the gradual loss from the circulating blood of something responsible for maintaining normal capillary permeability, or else the gradual appearance in the blood of a toxic factor, which would perhaps be removed if the blood circulated through the entire body. If the blood employed is replaced by a fresh supply, edema is checked somewhat but eventually progresses once more. In this situation, as after the administration of ANTU, anoxia of the lung capillaries soon becomes a factor, since the alveoli and bronchioles become unable to conduct air on account of the transudate which enters them. The very acute pulmonary edema of neurogenic origin described by Cameron and De (6) is a further instance illustrating inception of the process by a single cause, but, here again, as edema is established anoxia becomes an added factor though, on account of the rapidity of progress, probably of insignificant importance.

It is apparently an ingenuous mistake to look for a single cause of lung edema. Just as in the regulation of blood flow through the lungs, many factors inherent in the lungs themselves are responsible for the maintenance of normal conditions, so, in relation to edema, several factors operate together to produce the condition.

The removal of transudates and exudates from the lungs is equal in importance to their production Certain principles are fundamentally important to absorption from the lungs. They may be listed as follows·

1. The surface area of the lung capillaries is enormous and their walls lie practically naked in the alveolar septa.

2. The pressure of the blood in the lung capillaries is low, 10 mm of Hg. This head of pressure for outward filtration is more than balanced by the colloid osmotic pressure of the blood plasma, which is 25–30 mm. of Hg. Every influence in the normal lungs is thus to hold water and solutes intravascularly and to induce absorption of

water which enters the alveoli. The capillaries are practically naked in the alveolar walls and the excessive element of colloid osmotic pressure renders them avid for water. It is possible to administer 500 cc of water fairly rapidly by intratracheal catheter to a large healthy dog and find no trace of this inundation in the lungs at the end of an hour. The water is rapidly excreted in the urine. If, however, solutions containing the blood proteins are given intratracheally to animals, it is easily shown that their absorption is extraordinarily slight (10, 11). There is no doubt that absorption of protein solutions, small though it is, becomes more rapid if artificial respiration is employed or if, after instilling the test solutions intratracheally, test animals are allowed to recover from anesthesia and move about naturally. Courtice and Simmonds (11) found that in anesthetized recumbent animals no protein is absorbed during the first five hours and only traces at the end of nine hours The fact, however, that proteins reaching the alveoli are absorbed has possible important bearing upon sensitization and asthmatic phenomena When foreign protein reaches the alveoli, it remains there for some time. If, as is frequently the case, the foreign protein is in solution the alveoli contain the equivalent of a transudate

In the presence of lung movement, some of this alveolar material undoubtedly drifts up into bronchi lined by ciliated epithelium, and is eventually expectorated or swallowed. The important point for us is that an individual inhaling foreign substances which are not absorbed by the lung capillaries gains a reservoir of material which may act directly on the smooth muscle of the air passages or may maintain a degree of allergic effect over a long period. These are issues to be discussed further when the physiology of the bronchioles or, better, the physiology of the smooth muscle in the lungs is examined in its broad significance.

3. The lungs possess a very large supply of lymphatics and this system undoubtedly removes not only most proteinized solutions but also foreign particles of visible dimensions But absorption by lymphatics is invariably slow It is a function so highly developed in the lungs and so important in normal and pathological states that a full chapter is devoted to it, and no details need to be attempted here

4 Absorption from the alveoli is promoted by phagocytes—mononuclear cells whose origin is still a matter for debate—polymorphonu-

clear leucocytes, and lymphocytes. All of these cells contribute to the lysis of protein in the alveoli, and produce products which can enter *the blood capillaries* In the main, however, lung phagocytes find their way into lymph capillaries and move on with the lymph stream, coming to rest in lymph nodes or drifting on into the blood.

Among mammals man is unique in that for a great part of each day *his lungs are in a vertical position*. Even when he lies down to sleep, he changes position constantly It requires general anesthesia or unconsciousness from disease or accident to induce complete bodily immobility over more than minutes of time The vast net of com*municating lung capillaries containing* blood under low pressure is, in actuality, a sort of lake through which fluid moves, not only because of the beat of the right ventricle but also—and to a marked degree—under the influence of gravity and of air pressure These are matters of great practical importance. I have pointed out that the balance between the pressures of air and blood in the chest makes each of them able to exclude the other. Thus, if the pulmonary veins are obstructed so that *blood accumulates in the chest*, the entrance of air into the alveoli is more difficult Larger breathing efforts are necessary to secure adequate ventilation But the large size of the vascular bed and the low resistance to distention give blood and air in the lungs an easy fluctuant relationship unrecognized in most ob- [illegible] g flat [illegible] This [illegible] from [illegible] there is [illegible] thing increased carbon dioxide, the *flow of blood* through the capillaries is slowly blocked by stasis and the dependent parts of the lungs are poorly, or not at all, circulated as compared with their normal state. If detectable substances are given intravenously to dogs which have been *anesthetized and supine for some time,* the blood containing such foreign solutions does not get through these capillary regions. [illegible] d to in- [illegible] r [illegible] the dependent and comparatively motionless part of the [illegible]

Fenn and his associates (14) have shown how readily blood may be excluded from the chest by tightening blood pressure cuffs on the

thighs to 60 mm. of Hg so as to impede venous return and store blood in the legs and, reciprocally, how easy it is by breathing air under moderate pressure through a mask to diminish the blood entering the lungs. The subject of such an experiment lay upon a teeter-board (Figure 13), made of plywood, so balanced that the foot of the board was slightly heavier than the head. The board was kept from sagging by a flat steel spring, S, the movements of which were recorded upon a smoked drum A volume record from the plethysmograph was written upon the same drum through a small volume recorder A typical experiment is shown in the tracings of Figure 14 In the upper curve it is evident that as soon as pressure breathing began there was a fall, indicating that the weight of the upper part of the body became less. The lower curve shows that with this change, the volume of the feet—measured through the plethysmograph—became correspondingly greater By the application of various corrections, it was calculated that the pressure breathing dis-

thrown by gravity into areas from which it cannot readily reach the pulmonary veins We have been accustomed to ascribing the "blackout" which occurs in aviators on making a sudden turn to enforced

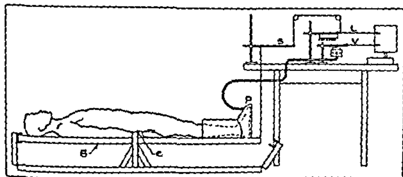


FIGURE 13 Diagram of teeter-board and plethysmograph methods B, board, P, plethysmograph, S, flat steel spring, L, lever recording level of teeter-board, V, volume recorder from plethysmograph (From FENN, W O, *et al* *Am J Physiol*, 1947, *151*, 259, Fig 1)

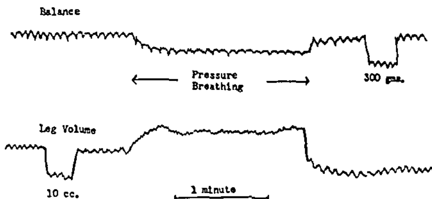


FIGURE 14 Effect of breathing air under 30 cm of water pressure. Pressure breathing began at the left end of the left arrow and ceased with the point of the right arrow. *Upper curve,* record from teeter-board *Lower curve,* leg volume recorded from plethysmograph (From FENN, W.O, *et al* *Am J Physiol*, 1947, *151*, 262, Fig 3)

pooling of blood in dependent parts of the systemic vessels. The black-out is accompanied by a sharp fall in blood pressure, and this, in the end, means insufficient blood is reaching the left ventricle. While pooling of blood in the systemic system may be the main physiological process in aviator's black-out, in considering this problem, we should not fail to keep in mind the readiness with which blood pools in different parts of the lungs, and the fact that imprisonment of blood in the pulmonary circulation can cause as prompt and effective reduction of left ventricular output as failure of blood to reach the right ventricle.

Realization of the ease with which blood moves from the lower part of the body into the lungs, and *vice versa,* has vital bearing upon the procedures one may use in resuscitation. The patient requiring assistance usually needs as free a flow of blood to the heart as can be secured for him. Obviously the head-down position, with the body resting prone or supine at an angle of about 35°, will promote flow of blood into the chest. The rhythmic pressure upon the abdominal viscera employed in the prone pressure method of artificial respiration will further force blood toward the heart, and when the pressure is released, the expansion of the thorax will suck more blood into this region. If a moribund, nonbreathing patient with low blood pressure is placed in a body respirator and the appliance tilted head

down, ideal conditions are provided to better the circulation In this case inspiration is secured by the normal process of chest expansion, and expiration follows passively. Increased negative pressure in the thorax promotes blood flow to the heart

But the patient requiring resuscitation needs rapid assistance above all else, and any such complicated resource as the respirator is out of the question It is pre-eminently important to get oxygen, as air or as the pure gas, into the lungs For many years men have been interested in doing this by some means which blows air or oxygen into the lungs through the nose and mouth via a face mask There has been incessant controversy as to the utility and safety of the rather complicated devices which have been manufactured to achieve this In every case inspiration is produced by positive pressure, which in each blast reaches about 14 mm Hg (19 cm of water) in the face mask and trachea The pressure is, of course, much lower in the alveoli, but to get air in, the lungs must be inflated by driving down the diaphragm and raising the ribs This positive pressure will force blood from the lungs to the heart, and, as the intra-abdominal pressure is slightly increased by lowering the diaphragm, blood in this region will be squeezed into the large vessels and toward the chest, into which it will run freely as the inspiratory blow is finished

Since men are vastly intrigued by mechanical devices, and since the engineers who have developed appliances designed to produce ventilation by blowing air into the lungs are obsessed with the idea that a pump should both blow and suck, it is natural that efforts have been made to apply suction for the production of expiration It is abnormal to produce inspiration by positive pressure, but if a safety valve on the appliance prevents the pressure from becoming too great, and if the air passages are unobstructed, air or oxygen can be forced into the alveoli by such means There is, however, no vestige of gain from applying suction to secure expiration This phase of breathing is normally passive, even when respiration is very violent When a positive pressure inflation of the lungs is finished, the chest, by elastic recoil, returns at once to its normal expiratory size Suction to get air out will not increase the rate or the volume of expiration If it has a value of more than −2 to −5 mm. of Hg, this abnormal suction element in the respiratory process apparently may increase

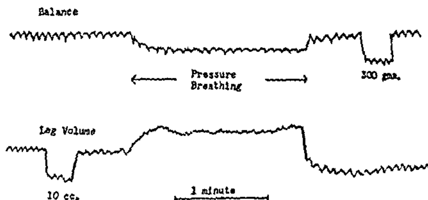


FIGURE 14 Effect of breathing air under 30 cm. of water pressure. Pressure breathing began at the left end of the left arrow and ceased with the point of the right arrow *Upper curve, record from teeter-board. Lower curve, leg volume recorded from plethysmograph.* (From FENN, W.O, *et al* *Am J Physiol*, 1947, *151*, 262, Fig 3)

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cent years, a new method has been widely adopted This procedure, suggested in 1932 by a Dane, Holger Nielson, places the victim prone with arms extended and palms under the head The operator raises the upper arms rhythmically, thus raising the ribs and lengthening the chest. This induces inspiration in a very effective manner For details, the reader is referred to a recent paper by the present author (17).

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transudation from alveolar capillaries and promote pulmonary edema

The fact that in death breathing generally ceases before the heart beat has naturally focused attention upon methods to sustain and restore respiration Over many years countless methods of artificial respiration have been suggested and given trial. It was realized years ago that time is the great factor in success. A man who has ceased to breathe has at the most twelve minutes to live before the heart stops beating, and five to seven minutes are nearer in accord with usual experience. No one can count upon obtaining and starting a mechanical appliance in so short a time Machines for artificial respiration are appliances for continuing breathing in cases in which manual artificial respiration has become difficult or impossible. All the mechanical "resuscitators" cause a movement of blood into and through the lungs, but this movement is little greater than that achieved by the prone pressure method of artificial respiration with the patient's body inclined head downward.

Finally, it is pertinent to cite two recent papers on artificial respiration by Gordon and his associates (15, 16). These investigators compared the amount of ventilation of the lungs resulting from different manual methods of resuscitation and from selected "resuscitators" which blew air into the lungs to produce inspiration and sucked it out for expiration As subjects, they employed volunteers whose breathing was stopped momentarily and the bodies of persons just pronounced dead but still warm and not in rigor. It is of great interest that artificial respiration employing a movement which actively expands the chest, as when the arms are pulled forward in the Silvester method, followed by chest compression, as in the Schafer procedure, produced excellent ventilation, quite equal to that of natural breathing. The resuscitators tested accomplished the same amounts of air movement Gordon's papers are accompanied by excellent bibliographies on artificial respiration and are a substantial contribution in a field which has been very controversial, and which has lacked decisive observations such as these of Gordon and his associates

The methods of manual artificial respiration described to this point and very widely used have employed a positive movement to force air out of the lungs and have expected return of air, or inspiration, to occur as a result of the elastic recoil of the compressed parts. In re-

III

THE BRONCHI AND BRONCHIOLES

CONTRACTION AND RELAXATION ASTHMA

THE HUMAN respiratory tract changes often in gross and histological structure from the nasopharynx to the alveoli. With these changes, there are differences in physiological performance which are of fundamental consequence in medicine and in surgery For example, though the nasopharynx is outside the scope of this monograph, the nasopharyngeal mucous membrane is composed of a surface layer of rather solid stratified epithelium, which is ciliated where air impinges upon it during inspiration The cilia have been shown to whip particles entrained upon them towards regions where the particles will be swallowed, lost by nose blowing, or spat out The entire area is in intimate contact with the outside world One's first sensations in "catching cold" may arise from inflammatory reactions involving sensory nerves in this general region It is known very definitely that over the olfactory area of the nasopharyngeal mucosa there is very rapid absorption from the surface, not only of salt solutions, but also of large molecules, even of particles visible microscopically This is absorption into the body of foreign material from the surface, not of material which has penetrated into the mucous membrane and is thus in direct contact with widely distributed blood and lymph capillaries

When, however, the trachea is reached, the ciliated columnar epithelium is singularly resistant as an absorbing surface, and until infectious processes really become established within the mucous membrane, absorption is negligible The same columnar ciliated coat is present in the bronchi until bronchioles are reached which are 0 4 mm in diameter and absorption from its surface is negligible throughout In addition to ciliated cells, the epithelium contains goblet cells, which produce mucus and which, in their turn, cease to be present when bronchioli of about 0 3 mm diameter are reached While it has been shown that very fine particles of carbon deposited upon the tracheobronchial surface may to some degree penetrat

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The anatomical structure of the airway from a bronchiole to an lveolus is shown in the reconstruction pictured in Figure 15 The ands of smooth muscle are arranged over the surface in lines so as o produce contraction and to withstand pressure with maximal fficiency Numerous elastic fibers run, in the main longitudinally, nder the encircling smooth muscle and eventually become part of he alveolar wall Figure 16 is a cast of an alveolar duct which

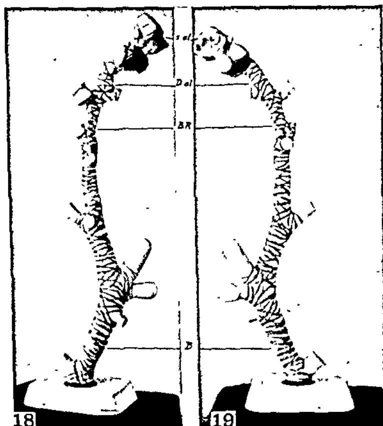


FIGURE 15. Reconstruction showing the distribution of bands of smooth muscle along a bronchiolus and its subdivisions Reverse views (From MILLER, W S *The Lung*, 2nd ed., Figs 20 and 21, p 32 Springfield Ill, Charles C Thomas, Publisher, 1947)

depths of the mucosa, this penetration is exceedingly slow. It is thus clear that man is well protected from his external environment through most of the upper respiratory tract.

So far as my knowledge goes, I think that those interested in clinical matters have paid too little attention to ciliary function. The usual patient with mild bronchiectasis greets each day with coughing, and soon begins to spit out glary mucus in which dust particles may be evident. This undesirable material has accumulated in bronchiectatic pockets and adjacent bronchi during the night. In the morning, with the patient's changes in position and volume of breathing, it is moved away from sites of origin; and certainly ciliary action must be important for eventual ejection from the lungs. We know too little about ciliary function. Anesthetics, such as chloroform, may diminish it and, at the same time, increase the production of mucus. The readiness with which ciliary cells are regenerated following the inhalation of destructive gases or after severe infection is not known, but has obvious importance for us.

Contraction and Relaxation

Until the bronchioles are reached, the airway repeatedly divides into two branches, and this simple type of division continues practically to the respiratory bronchiole, when more extensive division apparently occurs.

Cartilage, at first disposed in regular rings, eventually is found as irregular plaques, and, finally, when tubes of about 0 6 mm diameter are reached, disappears entirely and the airways lose "masonry" support for maintaining their diameter. Even where cartilage is present, the trachea and bronchi are readily lengthened, and muscle bands crossing the gaps in cartilage are capable of causing constriction, though relatively not so marked as in cartilage-free bronchi. Smooth muscle, disposed more or less circularly, together with elastic fibers, dominates the structure of the lower air passages. The muscle is well innervated by both vagi and sympathetics. It is a curious and interesting fact that, of all mammals, man and guinea pig are most copiously furnished with smooth muscle in the lungs, and this endowment apparently makes these two species particularly susceptible to periods of tonic bronchiolar constriction during which ventilation of the alveoli suffers.

(2) has described the manner in which the lung is altered in
between expiration and full inspiration His findings, shown grap
ically in Figure 20, seem quite simple As the chest expands and t
diaphragm descends, the lung is increased in volume from the cle

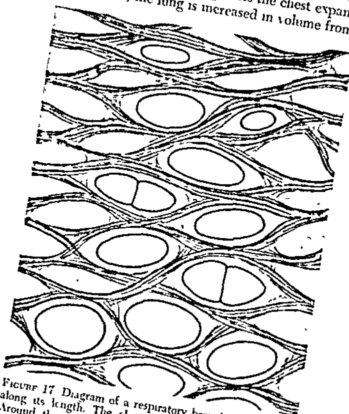


Figure 17 Diagram of a respiratory bronchiole, cut open along its length. The clear ovals correspond to alveoli Around them are interlocking fibers of smooth muscle elastic tissue, and collagenous strands (From Baltisberger W Ztschr f Anat u Entwckingsgesch, 1921, 61, 259 Abb 4)

area to that represented by the addition of the shaded area As this change occurs, the root of the lung descends and the bronchi are lengthened and increased in diameter The inspiratory lowering of the diaphragm is responsible for most of the lengthening, but it is easy to see that little change could be produced in the upper lobes

branches into alveolar sacs and alveoli. If the alveolar duct or respiratory bronchiole is laid open so that the inner surface and depth of the lining membrane may be examined, one finds an architecture such as is seen diagrammatically in Figure 17. The openings into alveolar sacs and alveoli are shown as clear ovals surrounded by interlacing fibers of smooth muscle, elastic tissue, and strands of collagenous material The actual disposition of smooth muscle as seen



FIGURE 16 Portion of a metal cast of a human lung showing an alveolar duct branching into alveolar sacs and alveoli After Bender (From MAXIMOW, A.A , and BLOOM, W *A Textbook of Histology*, 4th ed , Fig 407, p 471. Philadelphia, W B. Saunders Company, 1942)

in sections of the lung is shown in Figures 18 and 19 Figure 18 shows a sphincteric ring of smooth muscle in the wall of a fine bronchiole, Figure 19 has cut a ring of smooth muscle—showing as small black masses—just as alveoli are entered (1). It has been estimated that one cannot cut through a cubic millimeter of mammalian lung tissue without sectioning smooth muscle.

These complexities of smooth muscle and elastic tissue disposition in the lungs have been discussed in detail in order to give an idea of some of the factors involved in each respiratory movement. Macklin

even major adjustments. All organs having a smooth muscle c
operate physiologically at different sizes. One is most consci
of this in connection with the urinary bladder Under ordinary c
cumstances, the bladder fills with a large amount of urine befo
there is any requirement to empty it. But if the individual with

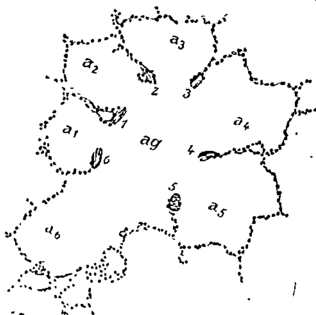


FIGURE 19 Cross section through an alveolar duct (ag) at origin of alveoli (a_1–a_6), showing transverse or obliquely cut rings of smooth muscle (1–6) (From BALTISBERGER, W *Ztschr f Anat u Entwckingsgesch*, 1921, *61*, 263, Abt 6)

moderately well-filled bladder is compelled to go out in the cold and becomes chilled, his bladder becomes a threat rather than a convenient storehouse. There is a changed state and a hollow organ, which has operated at fairly large size, has become a different organ It is not different in the way it acts but in its setting, in the fact that normal emptying must take place when a degree of filling

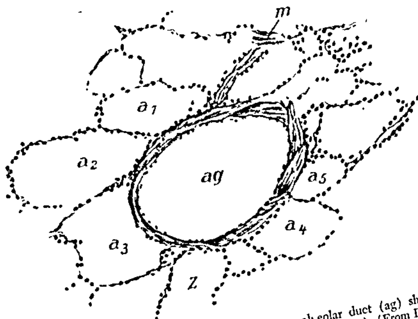


FIGURE 18 Slightly oblique section through an alveolar duct (ag) sh
ring of surrounding smooth muscle and adjacent alveoli (a_1–a_5). (From I
BERGER, W *Ztschr f Anat u Entwckingsgesch*, 1921, *61*, 263, A

if the root of the lung were immobile. Macklin's findings a
result of x-ray examinations of both man and animals The
logical adjustments which are involved in the changes are
tainly understood

It is easy to realize that the circularly disposed smooth
around the bronchioles and finer tubes to the alveolar duct
fectly arranged to cause contraction, and that relaxation,
results in expansion of the airway Unlike the gut, there
gitudinal smooth muscle, nothing to control length exc
fibers

The question as to why the bronchi and bronchioles
considerable equipment of smooth muscle which, app
often acts to produce contraction of high degree and th
of asthma must have an answer, for the body is not
produce illness but, on the contrary, to meet changing
quirements so smoothly that we are unaware of the o

has been reached clearly below usual capacity The organ performs in exactly the same way, whether at fairly large capacity or at much smaller size. Such changes are grouped under the unique physiological property called "tone"—a property expressed all through the body, but peculiarly evident in hollow organs well equipped with smooth muscle.

The lungs of a mammal seem far different from the urinary bladder. Yet, if one turns to the frog—a simpler creature which has done so much to promote physiological understanding—one finds the lung a single sac with a heavy coat of smooth muscle It is, in principle, a single huge alveolus with a typical capillary net upon the inner surface Slow changes in the size of this sac are characteristic The mammalian lung is again essentially a sac, though structurally so complex, and the bronchial system, the air-containing part, resembles the simple organ of the frog At rest, a man's minute volume of breathing is 8 to 10 liters With moderate exertion, it easily reaches 50 liters and may continue there for a long time The lung capable of 50-liter ventilation is a larger, but in no way a different, organ It operates efficiently at a new size

Let us now follow a single respiratory cycle (3) On inspiration, the diaphragm descends and with other voluntary muscles causes enlargement of the chest At the same time the voluntary muscle in the abdominal wall loses tone, thus reducing resistance to inspiration The highly elastic lungs follow the chest enlargement And it has been suggested that, accompanying the activity of the voluntary muscle, there is a reciprocal inhibition of bronchial smooth muscle, so that the air tubes are readily lengthened and widened to meet the need.

This is an attractive idea and involves reciprocal nervous control of voluntary and smooth muscle effectors but is not easy to apply Smooth muscle performs slowly It is eminently capable of operating at different lengths, but, so far as I know, it is not able to contract and relax with great rapidity I doubt, consequently, whether the lengthening and widening of the bronchi, which certainly occur during inspiration, are made possible by inhibition of smooth muscle tone A rate of breathing of 50 per minute, with fairly large volume at each breath, is readily attained, but this would mean rhythmic changes in length of smooth muscle cells too rapid to be

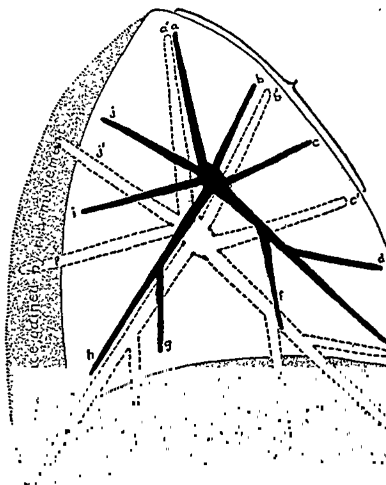


FIGURE 20 Diagrammatic representation of the bronchial tree with
able lung root Root shown from the side. All bronchi are free to
inspiration (broken lines), and shorten in expiration (solid blac
mitting the lung to expand equally in all directions (From MA
Am Rev Tuberc, 1932, 25, 404, Fig 4)

bronchial muscle The second type of reaction, again bronchospa depends upon sensitization of animals by subcutaneous injectio of a foreign protein which has no immediate effect upon bronch smooth muscle but which sensitizes the animal so that a second i jection after several weeks is followed promptly by bronchial co traction, often fatal. To illustrate the two types of reaction Hors serum administered intravenously has an immediate effect upon the bronchi of the guinea pig, sheep serum lacks direct toxicity, but when guinea pigs have been sensitized to it a second injection some time later is often fatal, and extreme constriction of the bronchioles is a major factor in causing death There can be little doubt that in the anaphylactic reaction something is formed which induces bronchospasm Man apparently suffers both from immediate effects of foreign protein on the smooth muscle of the bronchi and, more often, from the anaphylactic type of response

In attempting to analyze these reactions, one soon realizes that contraction of the pulmonary arterioles, and probably of the capillaries, usually accompanies the bronchiolar response and makes for greater danger to the animal involved There are other explanations for acute and chronic asthma The mucous glands in the bronchial mucosa are often hyperactive, and the respiratory difficulty in asthma is certainly due in part—perhaps in entirety—to blocking of even large bronchi by plugs of tenacious mucus In other instances, it is thought that rapid inflammatory swelling of the mucous membrane may shut off the bronchi.

In all three instances, it is characteristic that air in the alveoli, or air entering them during the reaction, is exhaled with great difficulty. This means that, in addition to the strain which may be imposed upon the right ventricle by sudden and generalized constriction of pulmonary arterioles, the high air pressure in the alveoli due to violent expiratory efforts also compresses blood vessels and further increases the load upon the heart Few of us realize adequately how serious a strain bronchial obstruction may be, whether due to spasm or to simple inflammatory swelling of the mucous membrane.

In October, 1948, the town of Donora in Pennsylvania experienced a disaster which illustrates my meaning. For five days and nights there was fog with absolutely no wind Smoke from residences

caused by nerve effects upon such tissue unless the smooth muscle in the bronchi possesses unique properties.

It is my belief that alterations in the length and diameter of the bronchi are caused by the power of the respiratory muscles, and do not, under normal circumstances, involve physiological reactions in the smooth muscle. The elastic tissue of the bronchial tubes is stretched during inspiration, and on expiration there is a simple sort of elastic recoil Smooth muscle is also highly elastic and does not interfere with this adjustment I believe that the bronchial smooth muscle—and, indeed, all of the widely distributed smooth muscle in the lungs—acts to enable perfect function at different lung sizes, and that the bronchial changes of inspiration and expiration are due to the muscles of respiration and to the perfection of capacity inherent in the elastic tissue of the normal lungs.

There seems no doubt that during inspiration the size of the alveoli alters so little as to be undetectable. When one recollects that the number of alveoli in man has been estimated at 750 million, it is not surprising that changes in size of individual air sacs have escaped us There is no question that the bronchioles down to the alveolar ducts expand and contract with each respiration, but this is attributable to elasticity and not to muscle action.

Asthma

The conception that the smooth muscle of the lungs acts, in the main, as a tonic regulator of lung size does not relieve us from the fact that this muscle is capable of fairly abrupt and sustained contraction irrespective of bodily requirements at the moment

Many agencies bring this about. Among them are vagal stimulation, histamine, foreign proteins, and anaphylaxis. Decided differences in reaction are found in different species. Thus, an intravenous injection of histamine in high dilution causes marked contraction of the bronchioles in the guinea pig (4). In the dog the reaction is far less The initiation of bronchial spasm in man and in some animals can be brought about in two ways. A solution of a foreign protein given intravenously may induce an immediate reaction. Not all proteins will do this, and some are effective in one species but of negligible consequence in others. When such responses do occur, there is no question of sensitization. It is a direct effect on

smaller bronchi and bronchioles This is a sort of peristalsis (5), initiated locally and expulsive in effect. Apparently stimuli are readily created by foreign material on the surface of the mucosa These stimuli cause the underlying smooth muscle to contract, with a resultant peristaltic wave which operates to clear the blocked airway It has been suggested that a gentle type of peristalsis goes on constantly and aids in alveolar ventilation Adrenin and allied sympathetic stimulants reduce the peristalsis or annul it, and the vagi, either by direct stimulation or through drug action, perhaps intensify it.

In this section on the air passages we come finally to the alveoli, about which much has already been said Let me recall the well-established fact of the existence of alveolar pores, that is, communications permitting passage of air and fluid between adjacent alveoli It is hard to assign any great benefit to the existence of these pores, but they have received so much attention it is proper to mention them There is no doubt that in normal quiet breathing lung lobules differ in the amount of ventilation How this variation is brought about, and how fluctuant it is from one part of the lungs to another are not known With increases in breathing, greater and greater uniformity of ventilation is attained Possibly alveolar pores are involved in this regulation of air flow but there is no direct evidence for it

Finally, the great advances in surgery which have made it safe to remove lung lobules and even an entire lung have turned us toward problems of the growth of lung tissue and regeneration after removal It is generally believed that we are born with our full number of alveoli The lungs increase in size, but not by multiplication of individual alveolar units Efforts to show that new alveoli develop in rats after lobectomy have not been convincing, but the techniques for alveolar enumeration per unit of lung tissue are far from satisfactory, and the subject demands new hands and new ideas It is certainly true that smooth muscle in the bronchial walls, in the blood vessels, and even in abnormal sites may at times proliferate markedly (6), but similar activity leading to the production of the highly specialized structure of the alveoli has not been observed.

and from industrial plants hung close to the ground, with no tendency to rise. Certainly the air contained nothing notably toxic, nothing save a trifling amount of sulphur dioxide and inert particulate matter On the fourth day, deaths began; and before a storm changed the atmosphere during the fifth night, twenty persons were dead and a number of others hospitalized. The episode was similar to the Meuse Valley experience in Belgium some years previously, where, in a wide area and under meteorological conditions of similar type, sixty deaths occurred between the third and fifth days. In the Belgium experience sulphur dioxide was easy to smell, but nothing of serious moment was ever detected in the air

Analysis of the Donora fatalities showed that all of the victims had histories of asthma, heart disease, or disease of the lungs, such as emphysema. Study of the episode brought out that practically everyone in the town had found the air heavy and unpleasant, and unescapable day or night. After four days of exposure, individuals with cardiovascular disease apparently experienced enough mild inflammation of the respiratory mucous membrane to bring about increasing dyspnea as a result of narrowing of the bronchial tubes Death resulted from cardiac failure. We must not forget that our success in prolonging life expectancy provides a very large reservoir of people who have no margin of safety; and confronted with an unremitting steady strain, such as atmospheric conditions in Donora provided, some of these persons become ill and die. It is significant that though the atmosphere remained unchanged there were no deaths in the last twenty-four hours. This fact perhaps indicates that by the end of several days the dangerously susceptible persons had succumbed.

Many efforts have been made to identify the toxic substance formed during anaphylactic shock. The similarity between the effects of histamine upon bronchi and lung vessels to what takes place in the anaphylactic seizure has made this compound receive much consideration. The fact, too, that the lungs are richer in histamine than are other organs has been thought of significance. On the whole, however, and after ample time for every sort of examination, I believe histamine has lost ground as the prime mover in the anaphylactic seizure.

There is another type of contractile reaction which occurs in the

IV

THE NERVES IN THE LUNGS AND THEIR EFFECTS ON BREATHING AND CIRCULATION*

NOTHING is of such fundamental importance to living creatures as a free and constant supply of oxygen The single source of this indispensable element is the air. It is not surprising that, as knowledge advances, it is found that more and more mechanisms in the body possess the means of asserting their need for oxygen In some cases, this need is far greater than in others. Some of the cells of the cerebral cortex, for example, are damaged irreversibly by seven to ten minutes of complete anoxia. In other regions, such as the intestines, over half an hour of deprivation of oxygen may fail to cause permanent harm, though for a time the tissue may be quite abnormal.

There is a center for breathing, a bilateral collection of nerve cells in the lower part of the pons and in the upper two-thirds of the medulla. This is true for man and for the dog and cat The cells in this grey reticulum are connected synaptically—that is, their fibers

physiology, showed many of the consequences to nerve impulses transmitted through contacts—that is, with an interface between the conducting fibers, as contrasted with conduction along an unbroken axone. But he did not realize how much further his conception would progress as the newer methods of physical chemistry began to be used in analyzing phenomena mediated through nerves For example, all of the newer literature upon transmission of nerve impulses from one nerve fiber to another, and from the ending of the fiber to the muscle or gland cell controlled by it, depends upon

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nerve impulses except smooth muscle in the bronchioles and in the blood vessels, and in the glands found in the bronchial epithelium Whether ciliary action, so important for movement of bronchial secretion, is under extrinsic nervous control is not known In all probability, ciliary action is dependent on chemical changes in the blood and on substances directly applied Anesthetics, such as chloroform, and sedatives depress ciliary movement, and thus delays bronchial excretion Small amounts of ether, ethylene, and alcohol apparently stimulate ciliary action (3).

The nerves of the lungs are both afferent and efferent, and arise from the vagi and from the sympathetic or thoracic division of the autonomic system. Larsell (4) found vasomotor nerves in the pleura distributed along branches of the pulmonary artery, and also larger fibers ending near the pleural surface, possibly afferent in function (5). The lung nerves with which we are most familiar are the vagal and sympathetic fibers ending in the bronchi, bronchioles, atria, and blood vessels Each lung receives an equal supply from each source, and, in addition, the bronchial walls contain many ganglion cells with fibers arranged as a sort of nerve net, not dissimilar to the plexuses of Auerbach and Meissner in the intestine. The function of these intrinisic nerves is not known, but certainly their presence makes complete denervation of the lungs quite impossible unless some drug should be found destructive to them

The peculiar gelatinous secretion produced by asthmatic patients and the more watery mucoid solution familiar in pulmonary inflammation is produced by cells in the bronchial mucous membrane, and is added to by protein-containing transudate from the capillaries in the bronchi It may well be that swelling of the bronchial mucosa and active secretion from the bronchial glands is under nervous control, but certainly no one has been able to demonstrate this, though the fact of abnormal secretion is familiar enough clinically (6, 7).

In connection with swelling and hyperemia of the bronchial mucous membrane, it must be remembered that the bronchial arteries are typically systemic vessels They follow the bronchi and branch into diffuse capillary nets in the tunica propria of the bronchioli These capillaries end before the alveoli are reached and are not concerned with respiratory exchange. At the end of the bronchiolus, they join capillaries from the pulmonary artery. True

the existence of interfaces where chemical and physical changes can occur without affecting the size or character of the impulse conducted by the axone.

The physiology of breathing in mammals owes much of its complexity to the fact that they have developed through a vast series of simple animals, first living in water, then partially in water, and only in comparatively recent years upon the land alone, taking along in their body fluids the essentials of the water existence they have forsaken. When life first began, the atmosphere was heavily loaded with carbon dioxide, and the solubility of this compound in water assured the necessity of living in an atmosphere very rich in carbon dioxide Carbon dioxide is vitally necessary to us, and is a constant excretory product of all living creatures, who must have oxygen to utilize the food they assimilate. It is not surprising to find that mammalian blood in land animals carries about 48 cc of carbon dioxide combined with it in various ways Of this amount, at sea level, only 3 cc. are dissolved in the plasma. Ten to 15 cc. are combined with hemoglobin of the red cells, and the rest is carried as bicarbonate in relatively fixed condition. Yet even this last carbon dioxide, released very slowly and inadequately from bicarbonate *in vacuo*, is liberated freely and rapidly through the action of an enzyme, carbonic anhydrase, found in the erythrocytes. Land-dwelling man is thus not so far removed from his carboniferous forebears as may seem to be the case; and it is not surprising that so diffusible a gas as carbon dioxide takes part in stimulating breathing At the same time, it has been shown that if the breathing of a mammal is made to depend solely upon carbon dioxide stimulation of the respiratory center by section of all the afferent nerves to this dominant collection of nerve cells, breathing becomes inco-ordinated, and the ability to increase and decrease ventilation smoothly and effectively is lost Under such circumstances, the land-dwelling mammal becomes as sluggish and helpless as was his remote ancestor who lived in the carbon dioxide-rich sea or upon the moist shores, where the atmospheric carbon dioxide was extremely high.

These facts make it essential to examine the effects of nerves on breathing, and the information gained has obvious place in understanding what occurs in inflammatory diseases of the lungs, such as pulmonary tuberculosis. The lungs contain nothing reactive to

nerve impulses except smooth muscle in the bronchioles and in the blood vessels, and in the glands found in the bronchial epithelium. Whether ciliary action, so important for movement of bronchial secretion, is under extrinsic nervous control is not known. In all probability, ciliary action is dependent on chemical changes in the blood and on substances directly applied. Anesthetics, such as chloroform, and sedatives depress ciliary movement, and this delays bronchial excretion. Small amounts of ether, ethylene, and alcohol apparently stimulate ciliary action (3).

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bronchial veins are found at the hilum of the lung, where they deliver their contents to one of the azygos or intercostal veins. Normally, anastomoses between the pulmonary arterioles and bronchial arterioles are of insignificant importance—a fortunate arrangement, since the higher pressure in the bronchial arterioles would give these vessels a commanding position in the delivery of blood to the alveoli and since their blood is arterial, nothing physiological would be accomplished Capillary anastomoses between the two circulations mean simply the mixing of systemic venous blood and that from the bronchioles, with resultant oxygenation of the entire supply As has been described in Chapter I, these anastomoses enlarge to become visible grossly. It is also apparently true that the vasa vasorum of the pulmonary artery are derived from the bronchial arteries.

Wounds of the larger branches of the bronchial arteries, owing to the high pressure of the blood within them, are very serious and may result in fatal hemorrhage or in a dissecting hemorrhagic infarction extending to the pleural surface In summary, what one must remember is that, in addition to the low pressure pulmonary circulation, the lungs possess an extensive systemic pressure circulation capable of the reactions seen in systemic arterioles and capillaries all over the body. Thus, if bronchial irritation occurs, dilatation of arterioles and capillaries, with eventual leakage from them, and swelling of the tissues may be expected. Such familiar vascular phenomena are now spoken of as reactive hyperemia, and are certainly of major importance in dealing with infection But no one can say whether or not the vastly larger pulmonary circulation is capable of any such reaction Indeed, aside from the fact that in abnormal conditions in the lungs, such as are found in bronchopneumonia, the arterioles and capillaries in the affected region are possibly dilated and certainly hyperpermeable—as expressed by the presence of coagulated plasma in the alveolar walls and spaces, together with accumulations of red and white cells—little is known of the reactivity of the finest branches of the pulmonary artery.

Figure 21 is a diagram of vagus and sympathetic fibers as they form the posterior pulmonary plexus and are distributed to the left lung (7) Both vagus and sympathetic fibers are afferent and efferent. The difficulty in unraveling the functions of the two systems

resides in the task of separating the fibers for functional analysis.

There is no doubt that stimulation of the distal end of one vagus results in equally distributed constriction of the larger bronchi and bronchioles, most pronounced on the side stimulated, but not absolutely limited to it. Furthermore, after vagal section paralytic dilatation of bronchioles occurs, but is not persistent

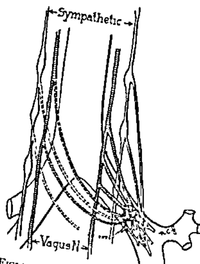


FIGURE 21 Schematic representation of the participation of both the sympathetic and the vagus fibers from the same side and from the opposite side in the formation of the posterior pulmonary plexus (according to Braeucker's experiments) (From PHILLIPS, E W, and SCOTT, W J M *Arch Surg*, 1929 19, 1130, Fig 1)

The efferent vagal fibers distributed below the larynx are constrictor for the bronchial and bronchiolar musculature and for the smooth muscle scattered through the lung tissue Possibly they activate the bronchial glands None of these functions is actually respiratory, that is, neither set of endings has a necessary part in the respiratory act, though both may modify it seriously, and do so under pathological conditions.

The vagal respiratory impulses which act in regulating breathing are afferent. They have their origin in nerve endings in the most distensible part of the alveolus—that is, in the walls of the alveolar ducts and atria just at the opening of the alveolus. The tissue carrying these endings is extremely thin, and is at the very beginning of the respiratory part of the lobule. Figure 22 displays the specialized nature of these receptors. Adrian (8) in 1933 accomplished the

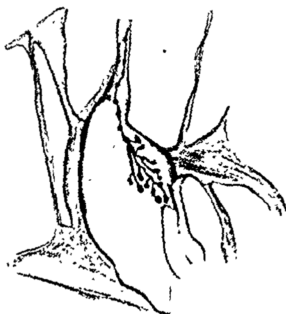


FIGURE 22 Free nerve ending in wall of atrium From a child 8 months old (From LARSELL, O, and DOW, R S *Am J Anat*, 1933, 52, 139, Fig. 14)

difficult technical feat of isolating four and even one vagus afferent fiber in the cat, and measured changes in potential—that is, the passage of nerve impulses in these simplified trunks. He found that on inflation of the lungs impulses start from the receptors in the alveolar ducts and atria and pass to the respiratory center, where they inhibit inspiration If the lungs are kept inflated, these inhibitory impulses continue to flow to the center; but if carbon dioxide accumulates as a result of apnea or if serious oxygen lack develops,

the center will break through, and inspiration will occur in spite of the continuous inflow of inhibitory impulses

When the lungs are deflated, a second set of impulses passes up the vagi, again from receptors practically in the alveoli, and these excite inspiration Such fibers go into action when a lung is collapsed by pneumothorax, and account to a degree for the immediate hyperpnea which may accompany such an experience

The modern conception of the respiratory center is that it is a bilateral collection of nerve cells, axones, and dendrites, constantly discharging nerve impulses to the muscles of respiration Lacking any inflowing nerve impulses, the respiratory muscles are forced into tetanic contraction (9, 10). As respiratory inflation proceeds, more and more inhibitory impulses bombard the center, and eventually inspiration passes over into passive expiration. In addition to the main volley of inhibitory impulses arising from the lungs themselves, inhibitory impulses reach the main or medullary part of the respiratory center from the pontile part of the structure, but these seem to be less effective than those from the lungs

It is of interest that the stimuli stopping inspiration and resulting in rhythmic breathing are caused by inflation of the lungs. In my opinion, this effect can be accomplished, not only by inspiratory inflation, but also by any influence which stretches the alveolar walls abruptly and tends to hold them in this position Thus, rapidly developing pulmonary edema caused by alpha-naphthyl thiourea (11), which induces thickening and relative inflexibility of the alveolar walls, results in hyperpnea The center continues to send impulses to the respiratory muscles, and the formation of these impulses is not restrained on account of the constant size and con-

and splints many of the alveoli in a fixed and expanded position. Again, hyperpnea results (12). Walsh (13), the last observer of this reaction, noted that the hyperpnea did not occur if the vagi were divided He used Adrian's methods for detecting afferent vagal impulses in isolated fibers, and came to the conclusion that impulses arising from receptors in small branches of the pulmonary artery might be responsible for the increased breathing. The problem is

thus unsettled, but, in any event, conditions producing hyperpnea by mechanical swelling and the stretching of alveolar walls must act abruptly, and must continue to act. When, as in cardiac failure, effects upon the lungs develop slowly and are complicated by changes in the oxygen and the hydrogen ion content of the blood, one cannot expect the abrupt onset of hyperpnea seen in such experiments as I have cited What has been described is essentially a Hering-Breuer reflex (14), very troublesome to students interested in the control of breathing ever since the reflex was described in 1868

The respiratory center is essentially inspiratory, and is inhibited by impulses passing up the vagi as the lungs are distended. A second bilateral collection of cells in the center excites inspiration when the lungs are overdeflated. In addition to these two sets of vagal endings, sensory fibers in the trigeminal and glossopharyngeal nerves and in the vagi are distributed to the mucous membrane of the pharynx, larynx, trachea, and bronchi; and, when irritated, produce a large inspiration, followed by a violent contraction of the muscles of expiration—that is, by a cough. It is noteworthy that the endings supplying afferent impulses resulting in cough are readily affected by anesthetics, while those concerned with the maintenance of breathing are resistant to anesthesia and to respiratory depressants Also it is important to realize that the normal [illegible] Irritant [illegible] asphyxi- [illegible] eathing than does air, until the blood begins to be poor in oxyg[illegible] and rich in carbon dioxide There is no evidence that cough is caused by secretions in the finest bronchioles, alveolar ducts, atria, or alveoli. Coughing begins when secretion has moved out of the respiratory part of the lobule Increased bronchiolar peristalsis apparently accompanies cough

The question as to whether pleural endings initiate cough is often asked. It is questionable if they do. The visceral pleura and lungs are practically insensitive to pain The parietal pleura, innervated by the intercostal nerves, is intensely sensitive. When a patient has a pulmonary embolus and experiences an infarct which involves the visceral surface of the pleura, transudation of plasma to this

surface occurs promptly, and the fibrinous coating begins at once to stick to the parietal pleura and to cause typical pleuritic pain on breathing. Cough begins later, and in the presence of the pleurisy may be exceedingly distressing. It means the movement of bloody exudate out of the infarcted area into bronchioles, and eventually into the sputum. Cough, under these circumstances, is associated with pleural involvement, but is not a reflex directly from the pleura

I am familiar with few direct studies on cough. Chevalier Jackson (15), in a bronchoscopic report upon cough, found about what one would expect. If an irritant was applied to the bronchial mucous membrane, cough occurred, but if the excitant was not moved nor the intensity of stimulation increased, the expiratory reflex—cough—slowly ceased

When it is understood that the respiratory center is automatically active in the constant discharge of impulses leading to inspiration, and that the cause of this automaticity resides in the metabolism of the cells that comprise the center, the physiological situation which results is not surprising Nerve impulses from many parts of the body affect the breathing rate and depth, but they do not initiate inspiration. In this connection, it has been found that hard muscular exercise induces a degree of breathing far greater than can be attained by inhalation of carbon dioxide or any respiratory stimulant (16). The stimulus to respiration of exercise apparently arises from receptors in the muscles and is quite independent of carbon dioxide production, oxygen lack, hydrogen ion concentration, or any of the conventional causes of hyperpnea

It is taken without question that where parasympathetic fibers—in this case, vagal—and sympathetic fibers innervate the same smooth muscle they will act oppositely. So far as the lungs are concerned, this principle is confused One would expect to counteract abnormal bronchiolar constriction, presumably due to the vagi, by injections of adrenin or any drug which stimulates the sympathetic nervous system Every one knows that within reasonable limits this is true But, to illustrate the confusion now controlling our ideas of the finer reactions within the lungs, I must point out that stimulation of the sympathetic components of the posterior pulmonary plexus often causes an appreciable degree of bronchoconstriction, just as comes from the vagi. No doubt the complicated and extensive relations

in this plexus account for some of the contradiction which exists. The facts seem to be that adrenin, ephedrine, and sympathetic mimetic drugs act upon the neuromuscular motor endings in the lungs, just as they do elsewhere, and one may rely upon them to relax bronchoconstriction in an asthmatic attack.

The arrangement of the pulmonary circulation is beautifully adapted to receive all the blood that is thrown into it by the right ventricle, and no matter what the course a red cell takes through the capillary net, the opportunity for gas exchange is much the same. The capillary surface area available in the lungs is huge, about 140 sq. M. The alveolar area for gas exchange is smaller, 90 sq. M, and the total number of alveoli in man is estimated to be about 750 million. At rest, about one-twentieth of their surface is used.

These data, coupled with the extreme elasticity of the lungs, lead us away from the conceptions of circulatory regulation operating upon the systemic side. The left ventricle is a powerful muscular pump, and it drives blood into a circulation which is essentially a system of shunts. Thus, if we exercise vigorously, the arterioles and capillaries in our legs dilate, and vessels which have been completely closed open to conduct blood. At the same time, similar vessels in the abdomen become constricted, thereby providing a suitable volume of blood to take care of the active regions. Such adjustments of the circulation are under the control of the vasomotor fibers of the sympathetic system. There is also in the capillaries and smallest arterioles provision for adaptive change in caliber independent of vasomotor regulation. This last sort of vascular change is to provide local increase in blood supply when the tissue involved is active. Thus, Krogh (17) showed that resting abdominal muscle in the guinea pig contained 70 to 92 capillaries per square millimeter which were open and carrying blood. The diaphragm, contracting normally at the time of the animal's death, had up to 2700 [illegible] (18) frogs single

glomerulus might increase in number during active diuresis.

Thus, whenever the activities of a tissue require more blood, not only is a freer supply shunted to it by vasomotor adjustments, but the vessels in the tissue involved undergo a receptive dilatation,

and capillaries, hithertofore closed, open, so that maximum working efficiency is assured This statement has not been proved for all tissues, but it is a fairly safe generalization.

Similarly, if a region in the skin is touched with a hot needle, pricked with a pin, or if for any reason a minute focus of infection begins to develop, all of the capillaries in the region involved become open for blood flow, and individual vessels dilate to an obvious degree.

In each of these examples, a part of the systemic circulation has required more blood The vessels co-operate in providing blood quite outside the reactions of the vasomotor system There are undoubtedly many causes of vasodilatation There are sympathetic vasodilator nerves. Acid metabolites cause relaxation of arterioles and capillaries, but the best explanation of the sharply defined dilatation seen in inflammation and in circumscribed local activity is the axone reflex In essentials, this reflex does not involve the spinal cord. It depends upon the existence of pain receptors—let us say, in the bronchial mucous membrane—in which originate impulses that travel towards the cord and are interpreted as pain. But the axones carrying these impulses branch, and twigs are supplied to the nearby arterioles and capillaries, which dilate as a result of their effect.

There is no doubt in my mind that axone reflexes account for inflammatory reactions in the nasopharynx, larynx, trachea, and large bronchi These regions are supplied by the systemic circulation, and they are highly sensitive to pain There is no doubt that the painful onset of a tracheitis or bronchitis, with swelling of the mucous membrane and transudation of watery fluid is highly typical of axone reflex causation.

The explanation of these useful changes in blood supply is still a matter for controversy. Thomas Lewis (19) believed that exercise, heat, cold, pain, indeed irritation of any sort caused the elaboration in the tissues of an H substance which acted directly on the capillaries, and a little later the discovery and exploitation of histamine provided a compound ideally ordered to act upon blood capillaries so as to produce the changes we call inflammation. Histamine proved to be a compound readily formed in most parts of the body. It was rapidly destroyed, but, while present, dilated blood capil-

laries and made them much more permeable It also contracted arterioles, but this action varied in different animals. Best, Dale, Dudley, and Thorpe (20) recovered histamine in large quantities from the lungs, particularly of the guinea pig, where the constrictor effect of histamine on the bronchioles can readily be great enough to kill the animal if even a very small intravenous injection is given Since histamine acts upon systemic arterioles and capillaries, it is reasonable to expect effects from it upon the vessels of the bronchial mucous membrane, which are systemic in origin And I have spoken of the axone reflex mechanism in inflammation of the bronchi and bronchioles, a mechanism in which histamine perhaps has part.

No one can say in what tissue of the lungs histamine arises (21), but certainly the commanding effects of the compound are exerted upon the bronchioles Since one of the effects of histamine is to increase capillary permeability, one might expect it to be a prime cause of pulmonary edema But pulmonary edema involves another circulation, and the respiratory pulmonary capillaries are quite separate from the systemic supply to the bronchioles. On stimulation of the vagal and sympathetic nerves to the lungs, effects upon the bronchi are readily elicited, but this is not true of the pulmonary circulation Adrenin injections and sympathetic stimulation may be shown to cause a trifling degree of constriction of the true lung vessels, but it is very insignificant, and one is left with the impression that the circulatory bed of the lungs is large enough to take care of all the blood supplied by the right ventricle. Moreover, the diffuse net of capillaries which surrounds each alveolus is so extensive and so evenly placed as to make no difference which branches in the net are conducting blood.

If the lung capillaries possess independent capacity to close and open, then we should expect histamine to affect the pulmonary circulation to a marked degree. But this has not been shown to be the case, unless at the same time constriction of the bronchi occurs (22). The most that can be said of the effects of histamine on the pulmonary circulation is that it has a slight constrictor effect on the pulmonary arterioles—enough to cause a trifling rise in blood pressure—but the more important effects, capillary dilatation and increased capillary permeability, have not been shown to take place. Efforts have been made to show that the lung capillaries have inde-

pendent powers of contraction and relaxation similar to the systemic vessels (23). Such experiments have required direct visualization of the alveolar capillaries in mammals, but are not convincing, since they have contained no assurance that the output of blood from the right ventricle remained unchanged when the pulmonary vessels under observation conducted or failed to conduct blood

The issues involved are not in the least academic. What I have been driving at is that in the final analysis of the pulmonary circulation we have as yet no reason to believe that the pulmonary capillaries behave like those in the systemic circulation It, thus, cannot be said with certainty that inflammation as it goes forward in areas of the lung serviced by the pulmonary circulation behaves in the same way as inflammation in regions of the systemic circuit In the bronchi and bronchioles, where the circulation is systemic, one's expectation of a characteristic active hyperemia will be realized, just as in the skin and other regions But the course of physiological events following injury or irritation to an alveolus is, I think, still unknown Is the respiratory circulation to the area shut off? Does it become more active? Or is it unaffected until progress of the injury causes actual harm to the tissue?

The active hyperemic reaction of inflammation is one of our oldest physiological experiences--quite as normal a reaction, in my opinion, as the secretion of gastric juice--but because it so often goes with destructive phenomena, it is relegated to the mercies of the pathologists We need to know the first physiological reactions when an irritant invades an alveolus, and at the present time our knowledge does not answer such questions.

There is a final point in regard to independent adaptive changes in the lung capillaries Whenever such changes occur in the systemic circulation, their purpose is to provide the area in question with [illegible]

normal lung over another. It is only when alveoli are subject to infection or irritation that one may think an increased supply of blood would be advantageous, but, as I have pointed out, there is no evidence that the pulmonary capillaries and arterioles display

the characteristic localized features of inflammation as seen in the case of the systemic vessels.

Where the capillaries from the bronchial artery join the true pulmonary capillaries—that is, at the beginning of the respiratory part of the lobule—there is a vascular region which is peculiar in that the systemic bronchial vessels connect suddenly with a vastly greater capillary bed than their own size and number warrant. It is probable that at the point of anastomosis the bronchial circulation slows to a considerable degree, and this may be the reason, as pointed out by Miller (24), that this transitional circulatory zone is a favorite site for the development of tubercles, both experimental and in human infections.

The Problem of Neurogenic Pulmonary Edema

For many years clinicians have described cases of pulmonary edema occurring abruptly and usually as terminal events in patients with some sort of cerebral disturbance. Weber and Blum (25), for example, described a case of hypoglycemic shock in a man of forty who went into "screaming coma" with opisthotonos. This patient gave clinical evidence of pulmonary edema, which was not relieved by treating the hypoglycemia, but an injection of hyoscine-atropine brought the severe attack to an end. This man had no disease of the heart, blood vessels, or lungs; and the conclusion was clear that the lung edema was of nervous origin. The authors cite a number of other cases, all with a background of nervous disturbance. The condition is known to be a rare but very serious complication of epilepsy, of cerebral wounds, of postencephalitic Parkinsonism, and of lesions of the brain stem Weber and Blum concluded that irritation of the vagus nerves was in some way involved; and in the case reported the relief gained from hyoscine and atropine bears out this explanation.

Cameron (26) has given a more thorough analysis of the problem presented by the literature, and points out that on the experimental side many of the methods used to produce pulmonary edema result in anoxia, irrespective of what has been done to nervous structures. But, again, this author is convinced that the condition can arise entirely from nervous sources. To this end, he and his collaborator

De (27) have produced conclusive evidence and have led us again to the vagus nerves as the responsible agents

At this point, it is worth while to consider something of what we know about the effects of nerves upon blood capillaries Vasodilator nerves produce widening of capillaries but unless some other factor, most notably anoxia of severe degree, is present, excessive leakage resulting in edema is not produced. It would seem that the varying needs of the tissues should result in the presence of nerves which in some way increase capillary leakage, but, with the exception of the kidney, where sympathetic nerve stimulation causes a sufficient narrowing of efferent glomerular capillaries to induce increased glomerular filtration, I know of no conclusive evidence in which such a result is induced by nervous influences. That is, nerves to capillaries do not induce changes in the endothelium which cause abnormal leakage of fluid A possible exception exists in the fact that irritation of pure sensory nerves—with the impulse traveling against the usual route, i e., away from the spinal cord—may produce vasodilatation and, after a time, abnormal leakage of fluid with local edema This is the background of certain cases of skin edema, urticaria of varying extent The lungs possess, in the vagi, nerves which induce a fair degree of vasoconstriction and a questionable amount of vasodilatation. That they have a prominent and much more elusive effect upon the permeability of the lung capillaries—an effect not seen except under very special conditions—thus endows them with unique properties.

There is no evidence which relates pulmonary edema to direct stimulus of the vagal fibers to the lungs, but it is not possible to stimulate these fibers without affecting the bronchioles—that is, to irritate vagal endings to the lung capillaries alone One can stop certain instances of pulmonary edema by vagal section, but one cannot initiate and maintain the condition through the vagi alone

In sharp contrast to the observations which indicated vagal stimulation as causing edema, are those of Faber (28) This investigator sectioned both vagi in rabbits and guinea pigs, being careful in the latter animals to spare the laryngeal nerves, so that aspiration of saliva was prevented Death occurred in three and a half to four hours and was preceded by the appearance of frothy saliva at the nose At autopsy there was severe pulmonary edema and congestion

the characteristic localized features of *inflammation as seen in the* case of the systemic vessels.

Where the capillaries from the bronchial artery join the true pulmonary capillaries—that is, at the beginning of the respiratory part of the lobule—there is a vascular region which is peculiar in that the systemic bronchial vessels connect suddenly with a vastly greater capillary bed than their own size and number warrant. It is probable that at the point of anastomosis the bronchial circulation slows to a considerable degree, and this may be the reason, as pointed out by Miller (24), that this transitional circulatory zone is a favorite site for the development of tubercles, both experimental and in human infections.

The Problem of Neurogenic Pulmonary Edema

For many years clinicians have described cases of pulmonary edema occurring abruptly and usually as terminal events in patients with some sort of cerebral disturbance. Weber and Blum (25), for example, described a case of hypoglycemic shock in a man of forty who went into "screaming coma" with opisthotonos. This patient gave clinical evidence of pulmonary edema, which was not relieved by treating the hypoglycemia, but an injection of hyoscine-atropine brought the severe attack to an end. This man had no disease of the heart, blood vessels, or lungs, and the conclusion was clear that the lung edema was of nervous origin. The authors cite a number of other cases, all with a background of nervous disturbance. The condition is known to be a rare but very serious complication of epilepsy, of cerebral wounds, of postencephalitic Parkinsonism, and of lesions of the brain stem. Weber and Blum concluded that irritation of the vagus nerves was in some way involved; and in the case reported the relief gained from hyoscine and atropine bears out this explanation.

Cameron (26) has given a more thorough analysis of the problem presented by the literature, and points out that on the experimental side many of the methods used to produce pulmonary edema result in anoxia, irrespective of what has been done to nervous structures. But, again, this author is convinced that the condition can arise entirely from nervous sources. To this end, he and his collaborator

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The animals were anesthetized with urethane and were given artificial respiration with air. Faber believed that the release of the strong tonic vasoconstrictor effect of the vagi caused capillary dilatation, blood stasis, and edema. It is not possible to explain these effects through the heart or general circulation. In this later day, one wonders whether—if there had been no anesthesia and less pooling of red cells in dependent capillaries—progressive blockage of vessels would have occurred, with consequent anoxia, increased capillary pressure, and edema. The experiment deserves further exploration, but does not certainly bear upon the possible direct effects of vagal endings in lung capillaries in causing the endothelium to become abnormally permeable.

Pulmonary edema is always an inauspicious development, and it is natural that a wealth of experimental work has been devoted to its explanation, particularly so on the neurological side of the problem. First of all, increased cerebrospinal pressure must be very great in order to produce edema; and vagal section checks its development The problem is made more difficult on account of the task of determining whether increased fluid in the lungs is inside or outside of the blood vessels. This is not the case when abnormal vascular leakage is well established, but it is very much of a problem when attempts are made to measure slight degrees of edema. Furthermore, such factors as inspiration of saliva and anoxia may enter the experiment and confuse the results There is, however, no point in discussing all the ways pulmonary edema has been produced. Massive or rapid infusions of salt solution bring it about, as one might expect. Such observations, however, have but one relation to the problem of neurogenic origin—namely, that the vagi apparently influence the process. Luisada and Sarnoff (29), in a series of papers, reported the production of lung edema in dogs by massive saline infusions given towards the head of the animal, coupled with stimulation of cardiovascular nerves Such experiments have value in showing that nerves can participate in the process, but they fail entirely in explaining why, in the presence of normal blood and with no heart or lung involvement, patients suddenly experience so dangerous a seizure as diffuse leakage of plasma into the alveoli.

Experiments directly applicable to the problem have been performed by Cameron and De (27). These investigators were en-

deavoring to produce hydrocephalus by internal injection of fibrin mixtures, when, to their surprise, the experimental animals in five to ten minutes developed fatal pulmonary edema Rabbits and rats were the animals employed, but the reaction was so uniform and so severe it seemed certain that other animals would be similarly affected It is an interesting expression of the elusiveness of the problem that Gamble and Patton (30) observed some degree of pulmonary edema after making small electrolytic lesions at the base of the brain in rats These authors did not know of the work of Cameron and De when their experiments were done and proceeded on the basis of admittedly vague clinical and experimental observations But it is certain that pulmonary edema of fatal severity can be produced rapidly in healthy animals by localized cerebral stimuli

Cameron and De have analyzed their experiments in considerable detail Figures 23 and 24, taken from their paper, show the location of the injection mass—in this instance, fibrin to which a small amount of India ink had been added to make it fully visible The summary of this important paper is worth quoting in full

"Acute pulmonary oedema can be produced experimentally by cisternal injection of a fibrin-forming mixture Whole blood or particulate suspensions such as India ink give similar though less constant effects. Records of the respiratory excursion, carotid blood pressure and right auricular pressure show that these undergo similar changes after severe tracheal obstruction, pulmonary embolism with starch granules and cisternal injection of fibrin with or without bilateral vagotomy, but only the last of these procedures is followed by acute pulmonary oedema These results suggest that neither asphyxia nor mechanical disturbance in the pulmonary circulation plays any part in the genesis of the oedema The stimulus for oedema production arises within the central nervous system, for the irritants cease to be active when they are injected extracisternally, when both vagus nerves are divided or their endings paralysed with atropine, or when cocaine is administered before the cisternal injection The increased cerebrospinal fluid pressure which follows the cisternal injection is not the oedema-producing stimulus It is suggested that the permeability of the lung capillaries may be modified by the outflow of stimuli from the brain stem by

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een so defi-
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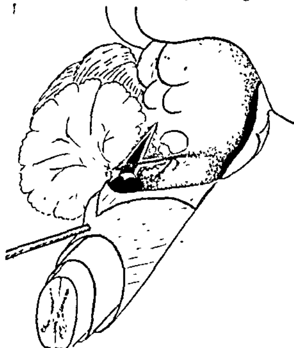


FIGURE 23 Diagram to illustrate the distribution of fibrin (black) in the basal cisternae, lateral recesses, and fourth ventricle after cisternal injection. A por- ... the ... cor- ... ath

laries—where they are certainly present—modify the permeability of the vessels, if true, is a unique physiological effect of vasomotor nerves

The Nerves in the Thoracic Wall

The nerves underlying the thoracic pleura arise mainly from the intercostals, and are characterized by their great sensitivity to pain.

They take no part in the normal physiology of breathing, but become a source of extreme distress in pleurisy and particularly in carcinoma when the apex of the lung is involved. Indeed, in apical carcinoma section of the posterior roots of nerves concerned may become necessary. The usual pain of pleurisy is experienced during breathing In self protection the patient, by remaining very quiet,

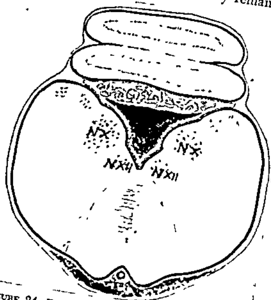


FIGURE 24 Diagram illustrating the relation of the fibrin clot to the dorsal nucleus of the vagus nerve (NX) in the floor of the fourth ventricle Frontal section (From CAMERON, G R, and DE, S N *J Path & Bact*, 1949, *61*, Fig 5, opposite p 382)

reduces his total ventilation as much as possible, and movement of the inflamed region may be restricted by lying upon it or by strapping, but I know of no reflex mechanism for reducing the motion of the affected side of a pleuritic chest.

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V

THE LYMPHATICS OF THE LUNGS AND PLEURAL SURFACES

THE LYMPH vascular system of the lungs resembles that of other parts of the body in that it is engaged constantly in the removal of extravascular substances which enter blood capillaries with difficulty, or not at all. The distinctive architecture of the lungs, the fact that so far as possible nothing is present except blood vessels and air spaces, plus an economical distribution of elastic fibers and smooth muscle, leaves but little space for lymphatics and lymph.

The pressure of the blood in the lung capillaries is low, 8 to 10 mm. of Hg, far below the colloid osmotic pressure of the blood, so that there is every tendency for prompt absorption of water and simple solutes

In the body generally, aside from the specialized task of absorbing fat from the intestine, the lymphatics are engaged in the continuous removal from the tissue fluid of blood protein derived from the blood plasma. If we except the flow of lymph from the intestines and liver, lymph is normally small in amount; and lung lymph is no exception to this fact.

The constituents of lymph enter this vascular system through the walls of lymphatic capillaries These walls consist of endothelial plates and are nowhere directly open to the tissue fluid In the lungs this means that the constituents of the lymph—water, salts, blood proteins, leucocytes, lymphocytes, occasional erythrocytes, and microscopically visible foreign particles—must pass through a cellular membrane before becoming part of the lymph The capillary endothelium of lymphatics has often been considered phagocytic, and even secretory, on account of the proteins and particulate material found in the lymph There is no evidence, however, that normal lymphatic endothelium ever possesses such functions Possibly, as in the case of blood vascular endothelium, the cells may display phagocytic power in areas of injury where regeneration is progressing rapidly. But such activity is the exception, and whatever lymphat-

ics contain must be understood to have been brought into the lymph by forces operating outside the vessels, and in no way due to powers inherent in and characteristic of the lining cells

Knowledge of the composition and flow of lymph in the human lung has been obtained by gross histological study of autopsy material, both from normal lungs and from lungs subject to disease. For example, the direction of flow of lymph toward the nodes at the lung root is gained by study of the direction of the valve leaflets in large draining lymphatics To this information from human material, a good deal can be added from experiments upon anesthetized animals, particularly dogs, where sufficiently large vessels for cannulation and lymph collection can be isolated

Anatomy

The lung lymphatics are said to exist as capillaries in the tissue surrounding the alveolar ducts This means that lymphatics are directly adjacent to respiratory epithelium only where respiration begins, and not about the atria and alveoli, the actual respiratory part of the lungs. Miller's diagram (Figure 1, opposite p 5) illustrates what is believed to be the case Here a plexus of lymphatics along a fine bronchiole and a pulmonary arteriole forms larger draining trunks, which accompany the bronchi and arteries and which communicate with a somewhat separate group of lymphatics along the pulmonary veins The lymph in this latter group of vessels flows, in the main, toward the root of the lungs. There is, however, a rich

flows toward the root of the lungs.

The lymphatics of the pleura are readily seen at autopsy in the lungs of city dwellers or of those whose work has exposed them to particle-filled air The large vessels, visible as a series of polyhedral rings, owe their conspicuousness to foreign particles which have been inhaled and which in some way have passed into the alveolar walls and eventually into lymph capillaries. If the lymph capillary empties into a larger lymphatic in the plexus of vessels associated with a vein, the particle may reach a pleural lymphatic, and by adhesion to the wall gradually outline the vessel so that it becomes

visible macroscopically (Figure 25). Between these large pleural vessels, which are well equipped with valves directing the lymph flow around the lung surface and preventing regurgitation into the depths of the lung, a finer irregular network of lymphatics is found. Many of these last vessels are of microscopic size and probably have little function unless pleural irritation is present.

To most observers of the lungs, the lymphatics are very inconspicuous; and the fact that the lymph vascular system in the lungs is one of the richest in the body is not recognized. The reconstructions of lung lymphatics made by Miller provide the best conception of

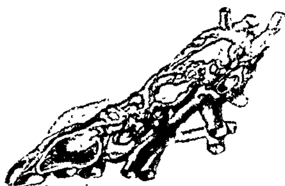


FIGURE 26 Plexus of lymphatics about a pulmonary vein (From MILLER, W S. *The Lung*, 2nd ed, Fig 75a, p 97 Springfield, Ill, Charles C Thomas, Publisher, 1947.)

the profusion of lymph vessels. Those in Figure 26 lie in the tissue surrounding a branch of a pulmonary vein. A very similar plexus of lymphatics is found about the bronchi and about the arteries. The usual appearance gained from sections, such as that of the bronchus shown in Figure 27, gives but a poor conception of the extent of the lymphatic system. The normal flow of lymph through such channels is slow and small in amount It is toward the lymph nodes at the root of the lungs and in the mediastinal tissues When lung edema occurs acutely, as in phosgene poisoning or after dosage with ANTU, lymph production is vastly increased Surrounding plexuses of lymphatics, such as are seen in Figures 26 and 27, become greatly

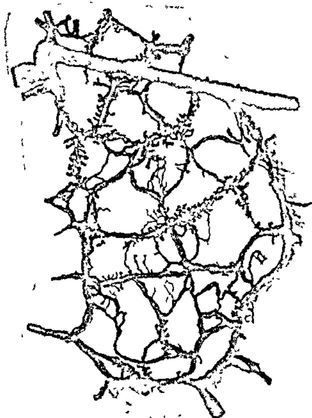


FIGURE 25 Lymphatic plexus in the pleura of a human lung Note that the large lobular vessels are connected by smaller branches, ordinarily not seen (From MILLER W S *The Lung* 2nd ed, Fig 76, p 99 Springfield Ill Charles C Thomas Publisher 1947)

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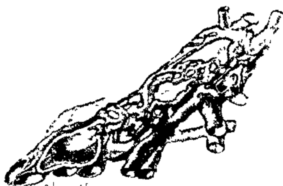


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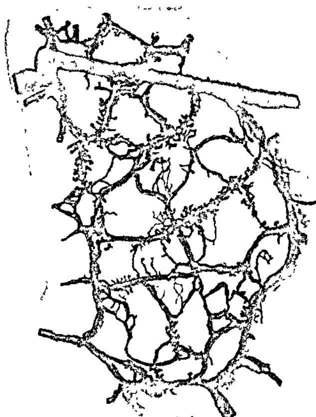


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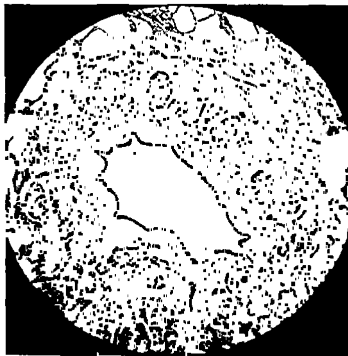


FIGURE 27 Lymphatics in the wall of a bronchus filled with cancer cells This figure illustrates in a striking manner the role the lymphatics play in the dissemination of disease processes in the lung (From MILLER, W S *The Lung*, 2nd ed, Fig 73, p 94 Springfield, Ill, Charles C Thomas, Publisher, 1947)

dilated, so that the individual tubes in the net are crowded together and a sleeve of lymph—often called a perivascular space—seems to surround the vein, the artery, or the bronchus upon which the vessels lie The valves in the lung lymphatics are not numerous and readily become incompetent Under normal conditions, they are so inconspicuous that they are said to be absent in the deep vessels When, for any reason, normal lymph flow is blocked, the fluid backs up in the larger trunks Lymphatics along the arteries and bronchi communicate with those along the veins, and these last, at the very surface of the lungs, communicate with the network in the pleura. It is thus inevitable that, given blockage, pleural thickening, exuda-

tion, and formation of adhesions follow. The effects of lymphatic obstruction, divested from those of acute inflammation, develop slowly, largely because the lymph drainage of any area is usually very extensive and consequently difficult to block. Such obstruction anywhere in the body is invariably attended by progressive growth of fibrous tissue, leading in many parts to elephantiasis. In my opinion, the essential lesion in pneumoconiosis is of the same sort. Blockage of lung lymphatics leads to deposition of fibrous tissue; and on the pleural surface this means pleural thickening and adhesions. Such changes interfere with the movements of the lungs and a respiratory handicap of varying extent ensues.

Physiology

The amount of lymph in the lung lymphatics is certainly variable and cannot be estimated. We do, however, know something about the flow of lung lymph and conditions causing and restraining it. Lymph is a derivative of blood plasma, which has leaked into the tissues through the capillary walls and has passed into capillary lymphatics. So far as is known, these capillary lymphatics possess an intact endothelial wall—that is, they are not in open communication with the tissues. I have pointed out that there are no lymph capillaries in the alveolar walls where blood capillaries are maximally numerous. It is thus apparent that water, salts, and proteins —derived from the blood—and alveolar inhaled foreign particles must often have a minute, but appreciable, period of travel in the lung tissue before a lymphatic is reached and the material finds its way through the endothelium into the vessel. In the case of inhaled particles, phagocytosis may be involved, material being ingested within the alveoli, carried by the cells into the tissues and then into the lymphatics, where these elements drift along to a lymph node and are entrapped. In the degree to which particles induce a chronic and inflammatory reaction in the lung tissues, in lymphatics, and in lymph nodes, some degree of blockage of lymph flow gradually takes place and lung fibrosis results

It is the usual idea that particles leaving the alveoli, and in some way becoming the cause of lung fibrosis, are first phagocytosed and get into the lymph stream by virtue of ameboid movement of phagocytes. To some degree, this may be true, but the fact that par-

ticles instilled into the alveoli may reach the lymph nodes at the lung root in less than an hour makes transit involving any degree of phagocytosis and ameboid movement beyond possibility Apparently, particles deposited on the surface of alveoli in breathing parts of the lung find their way into the lung tissue and into the lymph stream. In both areas they may be subject to phagocytosis, and when the lymph nodes are reached the particles are often intracellular.

The lungs contain numerous collections of lymphocytes unorganized into true lymph nodes Foreign body deposition occurs in and about such areas, and fibrosis develops We do not know the relation of these diffuse collections of lymphocytes to the lymph stream They usually occur at bifurcations of bronchi and blood vessels, and such points are favorite foci for fibrotic development

The lymph drainage of the lungs is peculiar in that practically all of the lung lymph enters the blood through the short and comparatively narrow right lymphatic duct The upper lobe of the left lung drains into the thoracic duct, and fairly frequently there are communications between the two sides One may instill into the lower left lobe, via the trachea, dog serum containing carbon particles and in a short while obtain the material from the right duct, while the thoracic duct remains entirely clear. This tendency to pass to the right may have some influence upon the incidence of chronic disease at the right apex, but no such hypothesis is proved It is true that there is a lymph node or several small nodes just at the entrance of the duct into the blood stream, which may readily filter out bacteria and become a focus of infection, but this possibility has not been demonstrated as fact and, for the time being, the tendency of the lymph to go to the right remains unexplained Doubtless there is an embryological reason for this peculiarity, which is altogether good fortune for the physiologist who wishes to collect lung lymph Right duct lymph also contains heart lymph, which is considerable in amount, but in the anesthetized animal cardiac activity is very steady and alterations in amount and composition of the lymph from the right duct may thus be ascribed to the lungs.

With very few exceptions, movements of lymph are due to movements of the lungs or to the pulsation of nearby blood vessels. If right-duct lymph is flowing under normal breathing, the flow prac-

tion, and formation of adhesions follow. The effects of lymphatic obstruction, divested from those of acute inflammation, develop slowly, largely because the lymph drainage of any area is usually very extensive and consequently difficult to block. Such obstruction anywhere in the body is invariably attended by progressive growth of fibrous tissue, leading in many parts to elephantiasis. In my opinion, the essential lesion in pneumoconiosis is of the same sort. Blockage of lung lymphatics leads to deposition of fibrous tissue; and on the pleural surface this means pleural thickening and adhesions. Such changes interfere with the movements of the lungs and a respiratory handicap of varying extent ensues.

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The amount of lymph in the lung lymphatics is certainly variable and cannot be estimated. We do, however, know something about the flow of lung lymph and conditions causing and restraining it Lymph is a derivative of blood plasma, which has leaked into the tissues through the capillary walls and has passed into capillary lymphatics. So far as is known, these capillary lymphatics possess an intact endothelial wall—that is, they are not in open communication with the tissues. I have pointed out that there are no lymph capillaries in the alveolar walls where blood capillaries are maximally numerous. It is thus apparent that water, salts, and proteins —derived from the blood—and alveolar inhaled foreign particles must often have a minute, but appreciable, period of travel in the lung tissue before a lymphatic is reached and the material finds its way through the endothelium into the vessel. In the case of inhaled particles, phagocytosis may be involved, material being ingested within the alveoli, carried by the cells into the tissues and then into the lymphatics, where these elements drift along to a lymph node and are entrapped. In the degree to which particles induce a chronic and inflammatory reaction in the lung tissues, in lymphatics, and in *lymph nodes, some degree* of blockage of lymph flow gradually takes place and lung fibrosis results.

It is the usual idea that particles leaving the alveoli, and in some way becoming the cause of lung fibrosis, are first phagocytosed and get into the lymph stream by virtue of ameboid movement of phagocytes. To some degree, this may be true; but the fact that par-

the lymph. Similarly, the highly diffusible antibiotics will reach the lung parenchyma and the lymph. Of more interest to us, is the problem of absorption of different solutions and of visible particles from the alveoli. In 1936, Fox (1) injected a variety of antisera intratracheally into rabbits and dogs He found that antibodies of three types in foreign or homologous serum appear very slowly in the blood stream and are retained in the lungs for a long time. Sterile inflammation of the lungs was induced by injecting starch-aleuronate suspension intratracheally on the assumption that absorption from inflamed tissue might be more rapid This did not prove to be the case

These experiments simply demonstrate the fact that watery solutions containing protein are removed in scant amounts and very slowly from the lungs They do not answer the question whether such absorption as does occur expresses direct entrance into the pulmonary blood capillaries or whether it is via the lymphatics

A year after Fox's report, Drinker, Warren, and MacLanahan (2), employing anesthetized dogs, injected horse serum, crystallized hemoglobin, and crystallized egg albumin into the trachea. Before injection they tied off the right lymphatic duct and cannulated the thoracic duct. Under these conditions, any material introduced into the trachea and eventually reaching the blood was almost certainly absorbed directly into the blood capillaries After an hour's time faint traces of the injected protein were occasionally found in the blood, but absorption by this route was very slight

Drinker and Hardenbergh (3) in a second set of experiments upon anesthetized dogs injected dog plasma, bovine serum albumin, egg albumin, crystalline hemoglobin in Ringer's solution, and finally glass spheres suspended in distilled water These spheres are readily seen microscopically in lung sections, and cannot be confused with the black particles found in the lungs of adult dogs In brief, their findings were that the absorption of all the protein solutions was slight and that the lymphatics were essentially responsible for it They felt that the principal barrier to entrance into the lung of protein-containing fluids in the alveoli was the "epithelial lining" of the alveolar sacs Whether or not there is a continuous cellular barrier lining the alveoli is open to question At the same time, it seems certain that something more than the blood capillary and lymphatic

tically ceases if one shifts to intratracheal insufflation without breathing *movements*. On the other hand, artificial respiration given through a tracheal cannula, with alternating blowing and sucking, produces a maximum flow of lung lymph, the lymphatics in the thoracic cage being massaged regularly by the movements of artificial respiration There is no doubt that intralymphatic material can be widely distributed through the lung tissue by the highly advocated resuscitators, which as they deliver air augment lymph and tissue fluid flow in the lungs to a degree little appreciated by those who advocate them

I have already pointed out that the amounts of lymph leaving the lungs to enter the blood are small. We have no idea what they may be in man, since so far as I know no one has had either the reason or the temerity to cannulate the human right lymphatic duct, and right duct fistulae, when they have occurred, have not been recognized Our impressions of the flow of lymph from the lungs are gained from experiments upon dogs, and while the flow per minute in a large and healthy dog is but a fraction of a cubic centimeter, it must be recollected that some degree of lymph flow in the lungs never ceases As long as breathing and heart beat continue, onward movement of lymph will go on, even if exceedingly slow In my opinion, lymph flow in the lungs, dependent as it is upon respiration and circulation, is a steadier phenomenon than lymph flow in other parts of the body—as, for example, the legs—where complete quiescence of the part may last for hours, during which time lymph flow is unrecognizable.

In protein content, lung lymph is usually about one-half that of the blood plasma from which it is formed In normal dogs, 3 7 per cent of protein in the lung lymph is an average amount If inflammation is present, this figure may rise to 6 5 per cent, or that of the blood plasma. Similarly, if the blood is diluted by saline infusion, the lymph protein concentration falls Albumin and globulin are present, their relative concentrations being those in blood

The low pressure in the pulmonary capillaries and the normal permeability of these vessels are so adjusted that very little transudation occurs It is, however, obvious that if readily diffusible substances, such as the sulfa drugs, are injected intravenously, they will leave the lung capillaries, enter the lung parenchyma, and eventually

begins to move through the lymphatics toward the nodes at the root of the lung The large phagocytes concerned in this migration may be arrested en route and, disintegrating, give up their particles, which, in turn, may be picked up by other phagocytic cells

This process of clearing the alveoli of particles and depositing them in the lung parenchyma, where they may initiate lung fibrosis, has dominated our thinking upon the pathogenesis of the pneumoconioses It is, of course, essential that particles become embedded in the lung tissue in order to cause fibrosis, and that once within the parenchyma the particles drift toward the root of the lung in the lung lymph It can be shown that if carmine particles, 4 μ or less in size, are deposited in the alveoli of a dog's lung they are found in lymph nodes at the lung root within an hour. This is too rapid a transit to have phagocytosis as an initial component Apparently, foreign material leaves the alveoli readily in the presence of breathing, much less readily if breathing movements are absent. Once in the lung tissue, whether in lymphatics or not, large phagocytes, similar to alveolar "dust cells," may ingest them, for such macrophages frequent the lymph stream and if they carry foreign particles are generally thought to have gathered them while intra-alveolar

The fact that foreign material collects in the lymphatics—which in their turn, reach lymph nodes before the lymph enters the blood stream—makes deposition of particles along lymphatics and in lung nodes inevitable, with eventual blockage and the possibility of fibrous tissue development, analogous to that seen in the limbs and dependent parts when lymph block occurs and elephantiatic change ensues.

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endothelium hinders absorption from alveoli to blood. Drinker and Hardenbergh could not find that their glass spheres reached either the blood or the lymph stream even after many hours, and this finding was not altered by vastly increasing lymph flow by means of intravenous injections of ANTU. Their experiments did show much phagocytosis of the glass particles, and in time this would have resulted in transportation of the particles to the lung root.

In another group of researches, Courtice and Simmonds (4), employing unanesthetized rabbits, also found the absorption of protein solutions from the alveoli very slow, but distinctly faster than in the presence of anesthesia. This difference is not explained by the authors, but emphasizes the fact that a normally breathing lung, accompanied by changes of position, is of major importance in promoting pulmonary absorption.

More recently Hahn and his associates (5, 6) injected radioactive silver colloids by means of a bronchoscope into the lungs of dogs They detected the radioactive colloid in substantial amounts in regional lymph nodes thirteen days after the injection. In as short a time as two days, there were traces of the silver in the lymph nodes The authors suggest that in metastasizing lung tumors this might be a useful method for treatment. Radioactive material injected into the trachea or into a large bronchus would be filtered out in the lymph nodes with tumor cells and would provide continuous dosage of the tumor.

Owing to the fact that many sorts of insoluble particles are constantly inhaled and reach the alveoli, from which they slowly disappear, the physician is necessarily interested in the way in which the alveoli become free of such foreign material; the relation of the size of the particles inhaled to the number reaching the alveoli; their chemical, crystallographic, or amorphous structure, etc. Each of these characteristics has been extensively investigated. In 1941, Robertson (7) published an excellent review and bibliography on the subject. For our present interest, it is sufficient to point out that particles as large as 12 μ may be inhaled into the alveoli, but the smaller the particles, the more easily this passage is accomplished. When the alveoli are reached, the particles may be phagocytosed and carried by the ingesting cells into the lung parenchyma, where lymphatics are entered, and the foreign material, still intracellular,

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